Circulation

FEBRUARY, 1957
VOL. XV NO. 2

OFFICIAL JOURNAL of the AMERICAN HEART ASSOCIATION

Editorial

Constrictive Pericarditis

CONSTRICTIVE pericarditis has a long and interesting history, but the present discussion summarizes the concepts developed during the last third of a century, specifically since the classic publication by Volhard and Schmieden in 1923.[1] By that date a number of operations had been successfully carried out in Europe. The first successful treatment of constrictive pericarditis by operation in the United States was reported by White and Churchill in 1930.[2] In the years since, knowledge of this disease has been progressively advanced by the observation of patients, by a study of the effects of various types of operation, and by physiologic measurements in man and in animals. These studies have made it possible to define the usual results of a constricting scar of the pericardium.

A long series of instructive physiologic studies has thrown light on the hemodynamic results of such a constricting scar. Examples are the studies of Sawyer and his associates[3] with the cardiac catheter and the ingenious experiments of Isaacs, Carter, and Haller[4] in producing constriction of each ventricle separately. These and other studies make it clear that while there may be some limitation to systolic emptying the major dysfunction in these patients is a restriction of diastolic filling. This restriction leads to a limited and essentially fixed stroke volume and to a persistent high ventricular filling pressure on both sides of the heart. This pressure is inevitably reflected in high venous and capillary pressures in both the peripheral and pulmonary circuits. The restricted stroke volume usually leads to a low cardiac output per minute in spite of tachycardia.

The new light on physiology and the accumulating experience of the years have led to a better understanding of the results of a constricting scar in terms of signs, symptoms, and the course of disease. Diagnosis is more accurate. The usual picture of constrictive pericarditis is now familiar: persistent congestion, low arterial pulse pressure, and a heart shadow that, while it may be moderately enlarged, is usually smaller than one expects for the degree of congestion present. Pulsus paradoxus may be observed. A third sound is often present, but murmurs are almost invariably absent and, if present and of higher grade than II, usually indicate an additional diagnosis of valve disease. Hypertension is not seen. Demonstrated calcification of the pericardium is helpful, but is present in only approximately half the patients.

Recent experience[5] indicated that diffuse myocardial fibrosis without pericardial abnormality may at times produce manifestations indistinguishable from those produced by constrictive pericarditis. Blount and his colleagues[6] have shown that the same may be said for extensive fibrosis of the endocardium. Cardiac catheterization does not serve to differentiate these disorders from constrictive pericarditis. The fact that the results of fibrosis in the myocardium or endocardium can so precisely imitate the results of fibrosis in the pericardium means that occasionally it is necessary to explore the pericardium surgically in order to be sure that the diagnosis of constrictive pericarditis is not missed and that no patient with this disease is denied the benefit of surgical treatment.

Hemodynamic studies indicate that the

major objective of surgery in constrictive pericarditis is the decortication and release of the 2 ventricles. No such clear evidence supports the position that the scars surrounding atria and great veins have comparable significance. The benefits of surgical treatment are substantial in most patients operated on for constrictive pericarditis, but they require analysis and appraisal. The writer's own experience with 66 patients, of whom 57 have been operated upon, leads him to the following conclusions.

Patients with constrictive pericarditis, if not treated by surgical therapy, show little tendency to improvement and tend to deteriorate gradually over the years.

On the other hand, most patients with constrictive pericarditis who are operated upon are improved and many return to normal or nearly normal activity. It is emphasized, however, that when such patients are followed with periodic quantitative measurements, few of them show restitution to entirely normal hemodynamics. Our own patients have been followed with measurements for periods up to 27 years since operation; almost all of them continue to show hemodynamic abnormalities, although almost all of them are able to work and lead nearly normal lives.

In our experience the degree of success realized from operation for constrictive pericarditis is determined chiefly by the following factors:

1. The type and extent of the operation, that is, the degree to which it has been possible to remove the constricting scar from the ventricles.

2. The presence or absence of continued activity of the causative infection.

3. The extent to which myocardial fibrosis complicates the constrictive pericarditis. Myocardial fibrosis may complicate as well as imitate a constricting scar of the pericardium. Some patients with constrictive pericarditis will not be improved by the most skillful resection of pericardial scar because they also have diffuse fibrosis of the myocardium. With present technics, fibrosis in the myocardium cannot be resected.

4. Fibrosis of the pleura or so-called constrictive pleuritis has been a factor in the postoperative disability of 50 per cent of our patients. In a few of these patients such disease of the pleura was the chief cause of residual disability after operation. In 3 patients it was a major factor causing death. Tuberculous pleuritis is a frequent accompaniment of acute tuberculous pericarditis and may lead to constrictive pleuritis. Hemothorax can also lead to pleural constriction; thus the operation that releases the heart may worsen the pleural disorder.

5. Changes in liver function may occur in patients with constrictive pericarditis, especially in those who have had severe and long-standing congestion. These changes in liver function may affect the health of these patients even after the relief of the pericardial constriction.

6. Various mechanisms associated with constrictive pericarditis lead some of these patients to develop persistent atrial fibrillation either before or after operation. This arrhythmia may be a factor in the long-term course.

7. Patients with a residual disability following an operation for constrictive pericarditis are affected by a long list of etiologically unrelated conditions that either impose a burden on the heart or interfere with its effective function. Examples of such conditions are obesity, pregnancy, valvular disease, renal disease, and chronic pulmonary disease.

8. Hypertension has a special relation to constrictive pericarditis. Practically speaking, hypertension does not occur when there is marked disability from constrictive pericarditis. Three of our patients, however, developed hypertension after successful operations for a constricting scar, and the hypertension has been an unfavorable factor in the long-term postoperative course.

Since the operation for constrictive pericarditis is in general not a curative procedure, but a modifying one, it is obvious that a knowledge of these various complicating factors is essential for effective management in the years following operation. It should be emphasized again that when the operation is adequate and when there is also informed management of the complicating factors, the outlook for normal activity on the part of patients with constrictive pericarditis is good.

Constrictive pericarditis is rarely if ever due to rheumatic carditis. The most frequent identifiable antecedent is tuberculous pericarditis. Most of our 66 patients developed constrictive pericarditis before the introduction of effective specific treatment for tuberculosis.

In the series of 18 patients studied by Andrews, Pickering, and Sellors[7] in whom the diagnosis of tuberculous pericarditis was made and whom it was possible to follow for an extended period, 16 eventually developed evidences of constrictive pericarditis. These patients were observed before the introduction of streptomycin.

On the other hand, Myers and Hamburger[8] treated 3 patients with streptomycin who were well, working, and had normal physical examinations, x-rays, and electrocardiograms at an average of 28 months after treatment. It is apparent, therefore, that prompt recognition of effective treatment may prevent the necessity for subsequent operation. It is equally clear that when tuberculous activity is discovered at the time of operation on the pericardium treatment should be instituted.

In summary, constrictive pericarditis can usually be recognized by relatively simple diagnostic procedures if it is thought of as a possibility. In a few instances an exploratory operation will be necessary to make an explicit diagnosis. When the diagnosis is correct, a substantial improvement is to be expected from operation plus perceptive management during the years after operation.

In patients with tuberculous pericarditis, the prevention of constrictive pericarditis is now a possibility.

C. Sidney Burwell

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If we begin with certainties, we shall end in doubts; but if we begin with doubts, and are patient in them, we shall end in certainties.—Bacon, 1561–1626.

The Lewis A. Conner Memorial Lecture

Functional Pathology of the Pulmonary Vascular Tree in Congenital Cardiac Disease

By JESSE E. EDWARDS, M.D.

While there are many anatomic varieties of congenital malformations of the heart and great vessels, most may be divided, from a functional point of view, into 3 types: (1) communication between the ventricles or between the aorta and pulmonary arteries, (2) anomalous drainage of pulmonary venous blood into the right atrium, and (3) obstruction to pulmonary venous flow. In each of these categories the responses of the pulmonary vascular tree have to be considered in understanding the altered dynamics. Depending on the type and degree of response in the pulmonary vascular bed, there may be a varying functional picture among patients having the same anatomic or functionally comparable malformation.

*"A teacher affects eternity; he can never tell where his influence stops."**

A PHYSICIAN with great vision and energy, Dr. Lewis A. Conner, was a leader in medical education and in preventive medicine. It is clear both from his writings and from conversations with one of his former interns, my good friend, Dr. Norman Keith, that Dr. Conner also had keen insight into the specific problems of the individual patient. He was a pioneer more than 40 years ago in emphasizing facts which then were controversial and which we accept today as commonplace. His interests in the pulmonary complications of the patient with typhoid fever led to a clear appreciation of the relationship of peripheral venous thrombosis to pulmonary embolism.

He indicated that peripheral venous thrombosis might be clinically latent and yet be responsible for pulmonary embolism.[1, 2] The pulmonary embolism might be recurrent and not necessarily fatal. In stressing these facts, he brought out the concept that in a patient with a disease seemingly unrelated to the lungs, there might be pulmonary manifestations that were, in fact, somehow related to the basic nonpulmonary disease.

With this background of the man for whom this lecture is named, and with my own personal interest in congenital cardiac disease, when invited to give this lecture I chose a subject that dealt with the interrelationship of the heart and the lungs. I believe this choice to be appropriate for this particular lecture, since, as we shall see, the pulmonary vessels play significant roles in many patients with congenital cardiac disease; patients in whom the primary difficulty is not pulmonary but rather is in another organ, as in this instance, the heart.

Historically, congenital cardiac disease may be divided into two periods separated in time and thought by two nearly simultaneous major developments. These were the reintroduction of cardiac catheterization by Cournand and Ranges[3] in 1941 and the devising of the anastomotic operation for pulmonary stenosis by Blalock and Taussig[4] in 1945. While there is some overlapping in approach between these two periods, they are, in general, rather sharply separated.

The earlier period began with anatomic description of the various malformations, a sphere in which Rokitansky made notable contributions and to which Sir Arthur Keith and Lev added materially.

The natural consequences of the establishment of various malformations anatomically were the attempts at clinicopathologic correlation. In this regard we readily think of Peacock,

Read at the meeting of the American Heart Association, Cincinnati, Ohio, October 26 to 31, 1956.

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Abstracted, Circulation **14:** 903, 1956.

* The Education of Henry Adams (Henry Brooks Adams). Chap. 20. 1907.

Fallot, the Gibsons, Roger and Brown. Coming from this era the clinicopathologic correlations of Maude Abbott, a pathologist, were classic and served to keep the light of congenital cardiac disease, however dim the flicker, from being extinguished. One cannot help realizing the personal satisfaction that had come to this devoted worker when, during the final years of her career, she witnessed a road to definite therapy. First came the attempted closure of a patent ductus arteriosus by Graybiel, Strieder, and Boyer[5] and finally the report in 1939 of success in such attempts by Gross and Hubbard.[6]

In the earlier of the 2 historical periods in congenital cardiac disease there was a strong tendency to attribute specific functional derangement to specific anatomic cardiac malformations. The outstanding exception to this was Abbott's teaching of the occurrence of *cyanose tardive*;[7] that is, patients with certain malformations might not be cyanotic for a period of time and then develop cyanosis. The basis for this change in function for a given patient was not clearly defined. Although some reference was made to a role that pulmonary vessels might play in such a change, no specific correlations between the changing clinical manifestations and functional or anatomic changes in the pulmonary vessels were forthcoming. In 1927, however, Moschcowitz[8] suggested that cyanosis in congenital cardiac disease might result from pulmonary hypertension.

The arrival of the second period in congenital cardiac disease was marked by a secure background regarding the anatomic nature of the various malformations but almost a complete void regarding the interrelationships between the pulmonary vessels on one hand and the function of the heart with the anatomic defect on the other.

That the pulmonary vessels might play a significant role in determining the behavior of the cardiovascular system in a given patient rapidly became apparent as some cyanotic patients on whom an anastomotic operation was to be done were found to have severe pulmonary hypertension, a condition that would not allow an increased pulmonary flow were the procedure done. Also, early in this period Bing's group[9, 10] and Dexter's group[11, 12] by the use of cardiac catheterization, studying patients with the same anatomic defect, found some to have normal pulmonary arterial pressures while in others the pulmonary pressure was as high as the systemic arterial pressure.

Such observations raised many questions: Is pulmonary hypertension a complication of certain types of congenital cardiac disease? Is it an integral part of the disease? Is the elevated pressure simply a product of altered function without changes in structure? Are there structural changes that accompany the elevated pulmonary resistance and pressure? If anatomic changes are present in the pulmonary vessels, are they the same in all cases with pulmonary hypertension? If differences in structure exist, are any of the changes potentially reversible with correction of the defect? Are any permanent?

Early attempts at answers to these questions were inhibited by inadequate material. What was needed was both histologic and physiologic data on a sufficient number of cases of any particular condition to reveal the entire story for that condition. By studying individual cases, even with pathologic and physiologic data at hand, one did not know just where he was with regard to the over-all manifestations of the condition. With the passage of time such accumulations have been made, notably by Dammann and his associates[13–15] and by the English workers Heath and Whitaker.[16]

From such organized studies, an orderly process becomes evident, so that now a number of the foregoing questions may be answered with confidence although mechanisms involved for certain phenomena are still lacking. Some of the questions still require conditional answers, but the stage is set for comprehensive understanding of the problem of the interrelationships between the pulmonary circulation and the heart which has one or another malformation. This leads us to appreciate that among a group of patients with the same anatomic diagnosis regarding the cardiac malformation, the physiologic and clinical behavior may be so diverse, depending on pulmonary vascular response, that superficially some patients could

hardly seem to be harboring the same malformation as others.[17–22]

One of our early experiences with the interrelationship of the pulmonary vessels and cardiac malformations concerned a 7-year-old girl who was observed in 1947. Dr. Howard B. Burchell, who had studied the patient clinically, thought that she had coarctation of the aorta proximal to a patent ductus arteriosus, and that the right ventricle was supplying blood to the descending aorta. The predicted anatomic arrangement was found at operation. The patient was one of the early cases of coarctation on whom operation was performed. Unfortunately, she died of hemothorax from separation of the aortic suture line on the thirteenth postoperative day.

Before the lungs were examined histologically, Dr. Burchell indicated that in view of his postulate that the right ventricle was supplying blood to the descending aorta, the pulmonary arterial pressure would have had to be equal to or in excess of aortic pressure. Was the high pulmonary vascular resistance necessary to maintain such a high pressure associated with structural change in the pulmonary vessels?

Histologic examination of the lungs revealed arteries that were so thick-walled they suggested the structure of peripheral systemic arteries. Our first reaction to describe these was the term "peripheralization" of the pulmonary vessels. After reflecting further on this, we recognized that the connections of the ductus and postulated direction of flow in this case after birth were like those in the normal fetus. This led us to postulate that the pulmonary vessels had not acquired a systemic arterial structure but that the changes were a carry-over into postnatal life of features normal in the fetus. Parenthetically, this case was one of four of coarctation and patent ductus arteriosus of which the pulmonary vessels were reported before this society at the 1948 meeting.[23]

I have derived much pleasure, encouragement, and guidance from the continuous interest that Dr. Burchell has evidenced in co-ordinating our pathologic findings with those of the clinician, physiologist, and surgeon. Much gratitude is due him for having been a major factor in making the story as organized in my mind as it now is.

However, should the audience judge that it is not organized, I must personally take the responsibility, not he.

Definition of Terms

There are 3 terms that are frequently used in a discussion of the dynamics of the pulmonary circulation: (1) pressure, (2) flow, and (3) resistance.

The first 2, pressure and flow, are real and measurable, while resistance is an abstract value derived from knowing the other 2. Yet the 3 are closely interrelated.

The level of pulmonary arterial pressure depends on the volume rate of pulmonary flow and the resistance to that flow. For a constant flow the pressure will vary directly with the resistance: the higher the resistance, the higher the pressure, and vice versa. For a constant resistance the pressure will vary with the flow: the higher the flow, the higher the pressure, and vice versa.

Pulmonary arterial hypertension refers to elevated pressure. A value of about 25 mm. of mercury, or about one fifth the systemic arterial pressure, is normal for pulmonary arterial systolic pressure. The dividing line between normal and abnormal values is not clear-cut. In many patients who have elevated pulmonary arterial pressure, however, the level of pressure is so high that the pulmonary arterial systolic pressure is about the same as the systemic arterial systolic pressure. At such equal levels the pulmonary arterial and systemic pressures are sometimes referred to as representing equivalent pressures.

A measured fall in pulmonary pressure without knowledge of the volume rate of flow does not tell us whether the observed phenomenon in pressure change is due to a lowering in flow, to a fall in resistance or both.

Certain Features of Normal Pulmonary Circulation

We are not concerned here with acquired cardiac disease, and so our discussion regarding the interrelationship between cardiac disease

and the pulmonary vessels cannot logically start with a normal postnatal pulmonary vascular tree.

We are, on the contrary, concerned with congenital diseases of the heart. These diseases are present both before and after birth and their relationship to the pulmonary vessels must therefore include a consideration of the responses of the pulmonary vascular tree in these various types of diseases during fetal life, at birth and in the postnatal state. To avoid consideration of events at the time of birth deprives us of an important link in the story.

With this background it is pertinent first to consider some of the features of the normal fetal circulation and the changes that take place at the time of birth and later.

Fetal Circulation

Blood returns to the heart by way of the 2 venae cavae (fig. 1*a*). Most of the superior caval blood flows through the tricuspid valve to the right ventricle.[24] The inferior caval stream splits at atrial level, some flowing through the foramen ovale into the left atrium, where it is joined by what blood returns through the pulmonary veins from the lungs. The mixture enters and leaves the left ventricle. Most of this blood is distributed to the branches of the aortic arch.

That part of the inferior caval blood that does not flow through the foramen ovale joins the superior caval blood, enters the right ventricle, then flows into the pulmonary trunk.

The principles concerned with distribution of the blood leaving the pulmonary trunk of the normal fetus are worthy of particular attention, since they are also applicable to those anomalies in which an abnormal communication exists between the lesser and the greater circulation.

In the fetus the pulmonary arterial bed is in free communication with the descending aorta by way of the ductus arteriosus. In view of this free communication the pressures in the pulmonary arteries and aorta and in the 2 ventricles are of the same magnitude.[25-27] Of the blood that leaves the right ventricle only a small proportion enters the pulmonary vascular

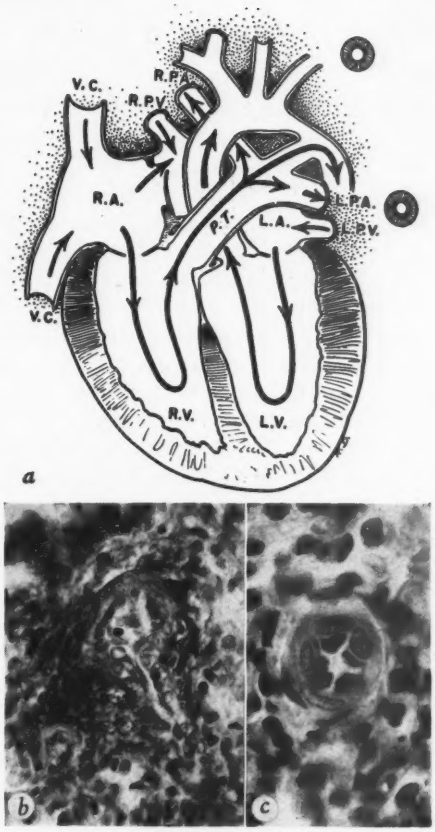

FIG. 1. *a*. Diagrammatic representation of the intracardiac circulation in the fetus. The circles beside the left pulmonary artery and the left subclavian artery indicate relative resistances to flow in the 2 systems. Here they are assumed to be equal. *b*. A small pulmonary muscular artery and arteriolar branch of a control stillborn full-term fetus. Characteristically the muscle of the mediae is thick and the lumina are narrow [ELVG (This abbreviation here and in subsequent illustrations indicates Verhoeff's elastic-tissue stain counterstained with van Gieson's connective-tissue stain.); reduced from × 500]. *c*. High-power view of pulmonary arteriole of a stillborn full-term fetus. The media is composed of thick muscle and the lumen is narrow (hematoxylin and eosin; reduced from × 900).

bed. The major part of it is propelled through the ductus arteriosus into the descending aorta and on to the placenta. In order for the flow through the ductus arteriosus to be possible, there must exist a high resistance to flow

through the pulmonary vascular bed. This high resistance is at one and the same time responsible for the pulmonary hypertension that is characteristic of the fetus and for right ventricular blood to be driven into the descending aorta.

The basis for the high resistance to pulmonary flow may in part be caused by the features associated with the collapsed lung,[27] and it may in part be brought about by action of the pulmonary arteriolar and arterial bed. The latter possibility is supported by the fact that in the normal fetus the pulmonary arteries and arterioles have thick muscular medial layers and narrow lumina[28] (fig. 1*b* and *c*).

The appearance of these small arterial vessels with their thick medial layers suggests that they are capable of significant degrees of vascular constriction, and the fact that their lumina are narrow suggests further that in the fetus the small pulmonary arterial vessels are in fact in a vasoconstricted state.

Changes at Birth

After birth the ductus arteriosus closes, at first functionally and later anatomically, thus eliminating the free communication between the 2 circuits at arterial level.[26, 29] Closure of the foramen ovale occurs almost simultaneously.[29, 30]

With these 2 fetal channels closed, there is complete partitioning of the 2 circulations, a circumstance that allows each to have its own resistance and pressure without affecting the flow through the other.

Early after birth the pulmonary pressure becomes lower than the systemic pressure and, since the same volume of blood flows through each circuit, the postnatal fall in pulmonary pressure has to be a consequence of a fall in pulmonary vascular resistance.[26]

While there is an abrupt fall in pulmonary vascular resistance at birth, the development of the fully established adult relationship between pulmonary and systemic resistance, wherein the pulmonary resistance is about one-fifth of the systemic resistance, is in part a gradual process. The latter opinion, until such time as direct observations are made, must rest on indirect, but presumably reliable evidence.

In the normal fetus the 2 ventricles are of about the same thickness. Usually by the end of the third postnatal month the adult disproportion between the thickness of the 2 ventricles is established both by anatomic and by electrocardiographic evidence (fig. 2*a* and *b*). The other supporting factor is that the thick pulmonary arteries and arterioles of the fetus gradually are transformed into the thin vessels of the adult (fig. 2*c*). The latter process is usually complete by about the age of 3 months but certainly by 6 months.[14, 28]

Adult Pulmonary Vascular Tree

We shall now consider the structure of the pulmonary vascular bed in the adult, both to contrast it with the fetus and also to have it serve as another point of reference in the consideration of the pulmonary vascular tree in the various congenital cardiac diseases.

There are 3 major categories of arterial vessels in the lungs as follows: (1) the elastic arteries, (2) the muscular arteries, and (3) the arterioles.

The elastic arteries are characterized by having numerous layers of elastic tissue arranged in a concentric manner identical with that in the aorta. Included as elastic pulmonary arteries are the pulmonary trunk and the various branches that accompany the cartilaginous bronchi. The smallest ones measure about 1 mm. in diameter. As in the aorta, there are collagenous fibers and smooth muscle cells between the elastic layers. The intima is a thin connective-tissue layer covered by endothelium. The adventitia is composed of dense collagen.

From the review of Burton[31] on the functional significance of the structural elements in walls of blood vessels, it is proper to consider that the elastic fibers of the elastic pulmonary arteries impart to this class of vessel a high degree of resistance to distention, while the relatively small amount of muscle would indicate that the elastic arteries have very little capability of actively constricting.

Arising from the elastic arteries is the next class of vessel, the muscular arteries. These vessels branch into lower orders of the same class of vessel. The muscular arteries are associated with the bronchioles, the respiratory bronchioles, and the alveolar ducts. The char-

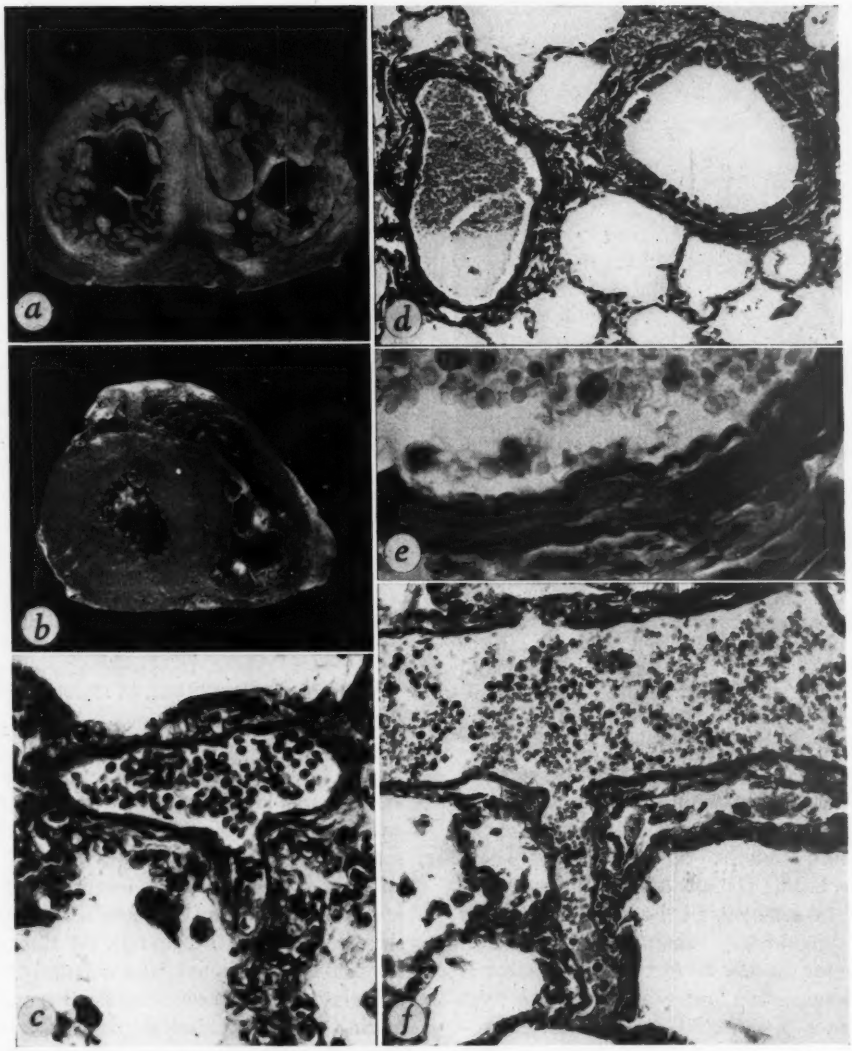

FIG. 2. *a*. Cross section of ventricles viewed from above in a control newborn infant. The 2 ventricles are of about the same thickness. *b*. Cross section of the ventricles in a control adult heart, showing the characteristic disproportion in thickness between the left ventricle and the right. This contrasts with the fetal state shown in *a*. *c*. A small pulmonary muscular artery and an arteriolar branch from a control 6-week-old infant. The thick media characteristic of similar vessels in the fetus has disappeared, leaving the adult type of change in which the walls are thin and the lumina are wide (ELVG; × 330). *d*, *e*, and *f*. From a control male patient aged 23 years. *d*. Large muscular artery and a bronchiole (ELVG; × 70). The arterial wall is thin and its lumen is wide. *e*. A segment of the artery illustrated in *d* (ELVG; × 570). *f*. An arteriole arising from a small muscular artery, each with characteristically thin walls and wide lumina. At the origin of the arteriole a small amount of muscle is present in the media (hematoxylin and eosin; × 200).

acteristic media of the elastic arteries changes fairly abruptly with the origin of the muscular branches. Two sheaths of elastic tissue from the elastic arteries enter a muscular artery to be the internal and external elastic laminae of that vessel. In that class of muscular arteries arising from the elastic arteries there may be additional laminae of elastic fibers, but these

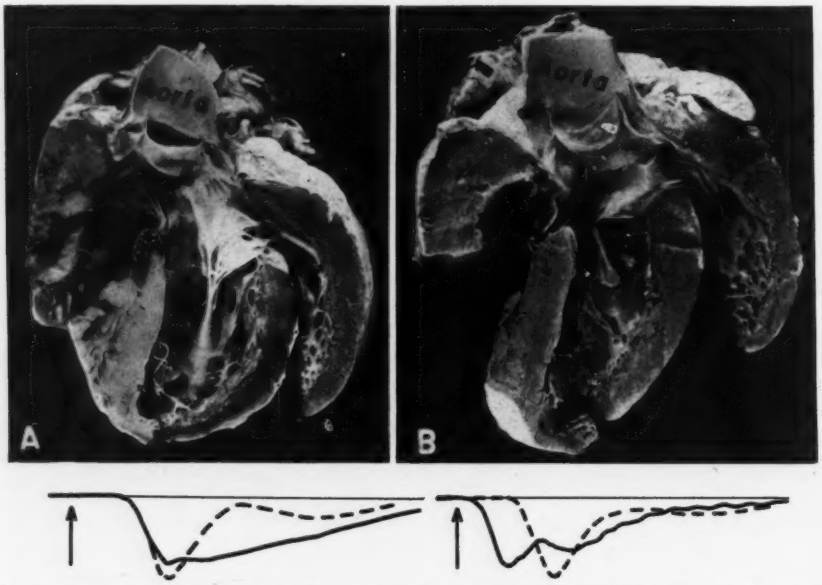

FIG. 3. Gross specimens and dye-dilution curves in 2 cases of ventricular septal defect, showing different hemodynamic features while the structure of the heart is essentially the same (solid curves for particular cases; dotted curves for anticipated normal). Total pulmonary resistance (dynes sec. cm.$^{-5}$) *A*. 305, *B*. 3197; systemic resistance (dynes sec. cm.$^{-5}$) *A*. 2500, *B*. 1886; pulmonary artery pressure (mm. Hg) *A*. 79/55, *B*. 135/83; radial artery pressure (mm. Hg) *A*. 93/62, *B*. 135/84.

are normally lost after further branching. In all classes of muscular arteries the major element of the artery lies between the internal and the external elastic membrane. This is a layer of the circularly oriented smooth muscle. There are a thin intima and a relatively thin adventitial layer of collagen. In the normal adult the wall of a pulmonary muscular artery is thin while the lumen is wide (fig. 3). The anatomic structure suggests a low resistance to flow; yet the presence of muscle suggests that a vasoconstrictive function may be found in the muscular arteries.

Arising from those muscular arteries which are related to the respiratory bronchioles are the muscular arterial branches which accompany the alveolar ducts. As the latter arteries are traced distally, they give off branches that arise about at right angles. The latter vessels are termed "arterioles." Beyond the origin of the arterioles the artery accompanying the alveolar duct loses its identifiable muscular media.

Here the vessel wall is composed of an endothelial layer lying on a thin layer of connective tissue that contains a single elastic layer. Beyond this level the arterial vessel communicates with the capillaries related to the air spaces.

The branches that are termed "arterioles" are small replicas of the arteries from which they arise (fig. 2*d*, *e*, and *f*). At their origins they have a media that has a circularly oriented thin layer of muscle. Shortly beyond their origins the arterioles lose identifiable muscle. Here they are composed of an endothelial lining, a small amount of supporting collagen, a single elastic layer, and a thin collagenous adventitia.

Our anatomic classification of the arterial vessels is similar to that of Brenner[32] with but one exception. By classifying vessels according to their caliber, segments which we would consider the proximal portions of arterioles would be classified as small arteries by Brenner's criterion, which indicates that the dividing line between small muscular arteries and arterioles is 100 microns. We have observed the proximal

part of vessels arising from arteries accompanying alveolar ducts to have diameters more than this in the normal, whereas the same class of vessel may have a considerably narrower diameter under abnormal conditions. Were one to apply a classification based on diameter, the same class of vessel would be called an artery in the normal and an arteriole in the abnormal. Furthermore, there are circumstances wherein an arteriole has a diameter less than 100 microns in the normal and in excess of this under certain abnormal conditions. From the foregoing it is apparent that there is in the lung a small class of vessel, which we call the arteriole. This has a muscular media at its origin and none in its remaining portion. Even at its thickest and muscular portion the normal arteriole of the adult has a very thin wall compared to the size of its lumen. A common ratio of lumen-to-wall thickness is about 8:1.

The pulmonary arteries and arterioles accompany and branch with the bronchial system, while the veins, as indicated by Miller,[33] are as far removed from the bronchial system as is possible within the anatomic confines of the respiratory units. On one side of the capillaries lie the arterioles, while on the opposite side lie the venules. The latter then proceed away from the bronchiole of their respiratory units toward the interlobular septum, where they join the venous trunks. Knowledge of this is particularly helpful, especially in studying single sections, since a thin-walled structure near an alveolar duct may suggest a venous structure, yet from its position the vessel must be of arterial or arteriolar nature.

If we were to judge functional potential from structural characteristics of the normal adult pulmonary arterial tree, with its thin walls and wide lumina, we could conclude that it is a low-resistance system. Functional observations in the normal indicate that this is the case.[34–38]

At the same time it is well to recognize that even in the normal the arterial side of the pulmonary circulation is more than a passive series of communications from the right ventricle to capillaries. Responses in the normal of increased resistance to flow when breathing gas mixtures low in oxygen suggest the possibility of a vasoconstrictive response.[39–43]

Vasodilatory effect may be observed in the normal pulmonary arteriolar bed, as judged by the fact that a significant increase in flow may not be associated with any appreciable rise in pressure. This can be accounted for only by a decrease in vascular resistance.[44, 45]

The same class of pulmonary vessel has so remarkably a different appearance from one patient to another that by study of individual sections one may not be certain that he is in fact comparing the same class of vessel. By serial sections, given classes of vessels may be identified by their origins and terminations and by their relations to the respiratory system.

While such studies are laborious, the assurance obtained when identifying a given class of vessel more than justifies the effort involved.

In our pathologic collection of congenital malformations of the heart and great vessels there are about 500 cases. In 96 of these, comprehensive cardiac catheterization studies had been done during life under the direction of Dr. E. H. Wood. In many of these the functional studies included obtaining multiple dye-dilution curves.[46–48]

I am indebted to Drs. Earl H. Wood, F. H. Helmholz, Jr., H. J. C. Swan, P. S. Hetzel, and I. J. Fox for making readily available to me the results of these various studies and for their helpfulness in reviewing these with me. In addition to reference to this specific material I have had free interchange of ideas with Dr. Wood and his group for some years, a fact which has given me a clearer insight into cardiovascular physiology than I would otherwise have had.

The major part of the presentation to follow is based on the cases in which functional studies had been done. In 50 of these, serial sections of pulmonary tissue were examined. Also, in a smaller number of cases that had not had physiologic studies similar sections were studied.

Functional Classification of Congenital Cardiac Disease

While there are many different anatomic types of cardiac anomalies, in most of these there is 1 of 2 anatomic derangements that place functional responsibility on the pul-

TABLE 1.—*Classification of Congenital Malformations of the Heart*

Functional category	Representative anatomic types
Communication between ventricles or systemic and pulmonary arteries	Ventricular septal defect, "tetralogy of Fallot," single functioning ventricle, patent ductus arteriosus
Pulmonary venous drainage into right atrium	Atrial septal defect, anomalous pulmonary venous connection
Pulmonary venous obstruction	Mitral stenosis, chronic left ventricular failure

monary vascular tree. One of the 2 anatomic derangements is an abnormal opening between the lesser and the greater circulation; the other is an abnormal obstruction somewhere in the circulatory system.

The abnormal opening may be at the level of the atrial septum, at the ventricular septum, or between the aorta and the pulmonary arterial system.

The important sites of obstruction may be anatomically located in the pulmonary arterial tract or in the mitral valve. More commonly there are defects other than mitral stenosis that produce essentially the same effect as though an anatomic site of obstruction had in fact been at the mitral valve. If the majority of congenital malformations of the heart are defined in a functional manner they fall into 3 major categories as shown in table 1.

VENTRICULAR SEPTAL DEFECT

I shall begin with a discussion of ventricular septal defect, realizing that what I say about this condition pertains in many ways also to patent ductus arteriosus.

When a ventricular septal defect exists, it is convenient to view this functionally as a communication not only between the ventricles but also between the left ventricle and the pulmonary arteries. It is proper at the outset to distinguish those cases of ventricular septal defect without gross pulmonary stenosis from those in which the defect is associated with pulmonary stenosis.

Ventricular Septal Defect without Pulmonary Stenosis

Three features of ventricular septal defect without pulmonary stenosis have occupied the minds of many in attempting to determine why the behavior in some cases differs significantly from that in others.

These features are (1) the relation of the aortic valve to the defect; (2) the size of the defect; (3) the pulmonary vascular changes.

1. Relation of the Aortic Valve to the Defect. Earlier teaching emphasized that the relation of the aortic valve to the defect represented an essential basic factor in difference of behavior among patients with ventricular defect. There is now sufficient evidence to indicate that these conclusions were based on insufficient examination of varied material, and are not valid.

The older concept stems principally from a review that Maude Abbott[49] made of a report by Eisenmenger.[50] The earlier author had reported the case of a cyanotic patient who at necropsy had a large ventricular septal defect and communication of the aorta, above the defect, with both ventricles. Abbott reasoned that the continuity of the right ventricle with the aorta would make a right-to-left shunt obligatory and named the combination of biventricular origin of the aorta above a ventricular septal defect without pulmonary stenosis and with cyanosis as the Eisenmenger complex. This name is in general use today for this combination of circumstances. In 7 of 8 cases with this anatomic arrangement she observed cyanosis. What Abbott failed to point out was that among many patients with the same anatomic arrangement between the aorta and the heart a right-to-left shunt does not occur. This negates the thesis that communication of the aorta above a ventricular septal defect with the right ventricle makes a right-to-left shunt obligatory.

Support for the present view is to be had from 2 representative cases illustrated in figure 3. In each, the anatomic relation of the aorta to the heart above a large ventricular septal defect was identical, showing free communication between the right ventricle and the aorta.

In each case the pulmonary arterial systolic pressure was essentially equivalent to that in the systemic arteries. Yet in one case there was a large left-to-right shunt and no right-to-left shunt. In the other case a significant right-to-left shunt was present, possibly associated with a small left-to-right shunt. Since the anatomic arrangements are the same in the 2 cases, th

reason for different behavior must be sought elsewhere than in the anatomic features of the malformation. This difference is found in the response of the pulmonary vascular tree, as suggested by Selzer and Laquer[51] and by Dexter and associates[11] and later by Dammann and associates[13, 15] and Blount and co-workers[22] among others.

In the first case the pulmonary vascular resistance, although mildly elevated, was significantly less than the systemic vascular resistance. In the second case the pulmonary vascular resistance was very high, being greater than systemic level.

We may therefore conclude that in ventricular septal defect the relation of the aorta to the right ventricle is not the primary factor in determining the direction of the shunt. Rather, the determining factor is the height of the pulmonary vascular resistance as compared to the resistance in the systemic circulation.

It is of interest to point out that Eisenmenger[52] himself, in a paper subsequent to the original one referred to by Abbott, indicated that in any case with defect of the ventricular septum lying near the aortic valve, the aorta is in communication with the right ventricle. He demonstrated that this situation could be reproduced even in a normal heart by artificially creating a defect near the aortic valve. This has been confirmed.[51, 53]

Simply by virtue of the fact that most ventricular septal defects are in close relationship with the aortic valve, it is likely that, in a random case of ventricular septal defect with a right-to-left shunt, the aorta will be found communicating with the right ventricle. However, if a defect is distant from the aortic orifice, as in a case described by Heath and associates,[54] the same dynamics may apply as when the defect is near the aorta. We have had similar experience.

The foregoing leads to the dilemma as to what to do about the term, "the Eisenmenger complex." Two avenues are open.

We may retain the term for those cases of ventricular septal defect with cyanosis, or we may discard it and indicate for such a case the descriptive designation, "ventricular septal defect with right-to-left shunt."

To do the latter would better convey the thought that the occurrence of a right-to-left shunt in a case of ventricular septal defect is simply one manifestation in the wide spectrum of functional behavior in ventricular septal defect and is not causally related to a specific anatomic type of ventricular septal defect.

2. Size of Defect. In each of the cases in the foregoing discussion the defect was large, and hence what influence the size of the defect had in one case was equally applicable to the other.

Small Defects. During fetal life, it is normal for the pressure in the 2 ventricles to be equal. At this time a ventricular septal defect, regardless of its size, is of little functional significance, there probably being very little flow through the abnormal opening.

After birth, when the tendency for pulmonary vascular resistance to fall is manifest, the size of the defect takes on paramount importance. A small defect, though an opening, is one that presents a high degree of resistance to flow through it (fig. 4*a*). It represents an obstruction between the left ventricle on one hand and the right ventricle and the pulmonary arteries on the other. In view of this obstruction the left ventricle obviously is not in free communication with the lesser circulation. It is possible for a differential in pressure to be built up between the 2 compartments. This happens[55, 56] as the pulmonary vascular resistance falls toward normal postnatal levels and a normal postnatal evolution of the pulmonary arteries and arterioles is manifest. The small defect is a controlling factor in preventing large volumes of blood from shunting from the left ventricle to the lesser circulation. The pulmonary and right ventricular pressures are normal.

Large Defects. Defects that have about the same diameter as the aorta are said to be large.[56] Allowing free communication between the left ventricle and the right ventricle and pulmonary arteries, they lack the obstructive character of the small defect (fig. 4*b* and *c*).

It is at this point important to recognize a principle of interrelationship between the 2 circulations when there is free communication between them. Burchell and Wood[57] and Hamilton and associates[58] have clearly demonstrated that the direction and volume of flow through such a communication depend principally on

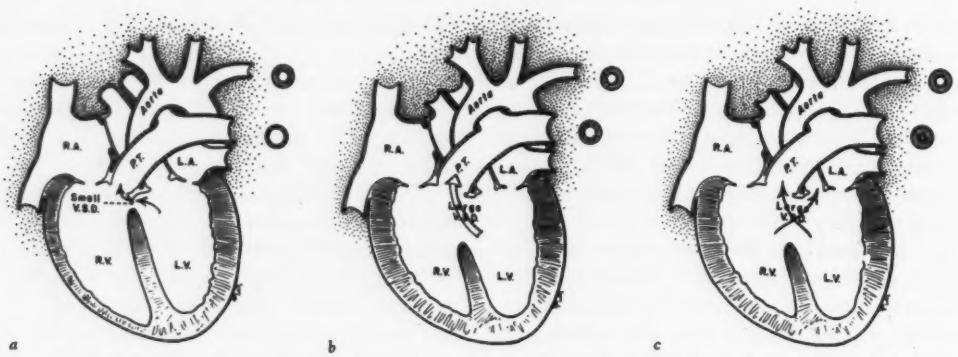

FIG. 4. Diagrammatic representation of hemodynamics in small (*a*) and large (*b* and *c*) ventricular septal defects. In the small defect the pulmonary resistance is significantly less than the systemic; the defect itself represents an obstruction. In the large defects, when the pulmonary resistance is less than the systemic a left-to-right shunt occurs. When the pulmonary resistance exceeds the systemic a right-to-left shunt appears.

relative resistances to flow in the pulmonary as compared to the systemic circulation. The blood flows into the system with the lower resistance.

The size of the defect determines whether it itself is an effective barrier between the left ventricle and the pulmonary arteries. When the defect is large, significant changes, both functional and structural, are evident in the pulmonary vascular tree.

3. Pulmonary Vascular Changes. After birth, without obstruction at the defect, and with pulmonary vascular resistance falling, there would be a tendency for a large runoff of left ventricular blood into the pulmonary circulation. If the pulmonary vascular resistance fell to normal adult levels, 2 possible lethal consequences of such a runoff might exist. In the presence of a defect so large that it exerts no obstruction between the ventricles, the systolic pressures in the 2 ventricles and in the systemic and pulmonary arteries approach identity.[59, 60] With left ventricular blood diverted to the pulmonary circulation and assuming that the systemic vascular resistance did not change, the resulting lowered flow to the systemic circulation would lead to a fall in systemic pressure. This might be so low as to result in inadequate perfusion of the tissues. The other possibility assumes that, though the systemic pressure would fall, it might still be high enough to perfuse the tissues adequately. However, the large volume shunted through the pulmonary circuit and back to the left ventricle might be responsible for left ventricular failure.

In acquired diseases such phenomena may occur. One or the other of these mechanisms may perhaps be the basis for early death in adult patients with myocardial infarction who suffer a large rupture of the ventricular septum. Likewise these factors may operate to cause early death in experimental animals in which ventricular septal defects beyond a certain size are created.[61] In each of the examples of acquired defects cited the pulmonary vessels are assumed to be of normal type with little muscle in the small arteries and arterioles.

With the sudden stimulus these pulmonary vessels are not structurally prepared to meet the sudden demand on them. Because of the lack of sufficient muscle for effective vasoconstriction they cannot produce a "protective" resistance.

Quite a different situation exists in the patient born with a large ventricular septal defect. At this time the pulmonary vessels are equipped with thick muscular coats and are capable of significant vasoconstriction and so of maintaining a higher-than-normal resistance to pulmonary flow. By this means the pulmonary vessels usually prevent a left-to-right shunt of such magnitude as would be lethal. At the same time it is recognized that even in the presence of a low pulmonary resistance a fall in systemic resistance would tend to reduce the magnitude of the left-to-right shunt.

Dammann and Ferencz[15] have traced the behavior of the vascular system in patients of varying ages with large ventricular septal defects. In the early postnatal months there seems to be an inherent tendency for the resistance to fall toward normal. After this the pulmonary vascular resistance tends to become stabilized at a level less than systemic resistance, but greater than normal pulmonary resistance. In time there may be a progressive rise in pulmonary vascular resistance. Divertie and Swan[62] in our physiology laboratory have made similar observations.

Since the direction and volume of flow through the large defect depend on relative resistances to flow through the pulmonary and systemic circulation, the early postnatal months when the resistance falls are particularly critical.[63] It is in this period that patients are particularly susceptible to death from left ventricular failure as a result of the large shunt. In later years when the pulmonary vascular resistance rises, the left-to-right shunt falls off in volume and may be superseded by or associated with a right-to-left shunt.

In cases with small ventricular septal defects the pulmonary vessels cannot be distinguished from the normal (fig. 5*a*). This correlates well with observations that with a small defect functional studies yield essentially normal values for resistance. In all cases with large defects that we have studied the pulmonary vessels are abnormal, although there are different kinds and degrees of change. In a given case 1 of 3 anatomic types of pulmonary vascular beds is encountered which may be called (1) high resistance-high reserve, (2) high resistance-low reserve, or (3) a form transitional between the first two.

The type of vascular bed termed "high resistance-high reserve" is essentially like that of the normal fetus. It has the following characteristics (fig. 5*b* and *c*).

The muscular arteries of all sizes show prominently thick muscular mediae associated with thick elastic laminae. At times there is increased thickness of the adventitia by dense collagen. The arterioles show prominently thick muscular medial layers and often well-defined elastic layers as well as suggestions of thickened adventitiae. The thickening of the medial muscular layer extends for varying distances down the length of the arterioles, but consistently the origins of the arterioles are the most strikingly involved by the medial thickening and luminal narrowing. At times the muscle fibers of the thickened arterioles have a vacuolated character.

Intimal fibrous lesions are usually absent or, if present, are few and restricted to small arteries or arterioles.

The reason why this type of vascular bed is characterized as a "high resistance-high reserve" system is that when measurements are available patients who have this type of bed as a group show resistances above normal adult levels. The basis for this seems to lie in vasoconstriction. The constricted vessels seem to have a potential for vasodilatation, thereby potentially decreasing the total pulmonary resistance or, stated otherwise, increasing the capacity of the bed.

Judging from the similarity in structure between the high resistance-high reserve pulmonary vascular bed in large ventricular septal defect on one hand and the bed of the normal fetus on the other, it seems probable that a decrease in pulmonary vascular resistance could occur after the abnormal communication between the 2 circulations is obliterated. The type of vascular bed that I have designated as having a high resistance-low reserve characteristic has a remarkably different appearance from that in the foregoing type. Here the large muscular arteries show characteristic obliterative intimal lesions (fig. 5*d*, *e* and *f* and fig. 6). The small muscular arteries and arterioles may show similar lesions, but the majority are thin-walled and dilated. The intimal lesions involve arteries as large as 300 microns in diameter. These lesions frequently show a plexiform arrangement in individual cross section. In serial sections, the involved segment of artery shows irregularly deposited collections of young connective tissue, creating a markedly narrowed lumen with irregular configuration. Older lesions are acellular and hyalinized. The irregular spaces in the lumen of the artery with intimal thickening may yield a picture suggesting organized thrombus.

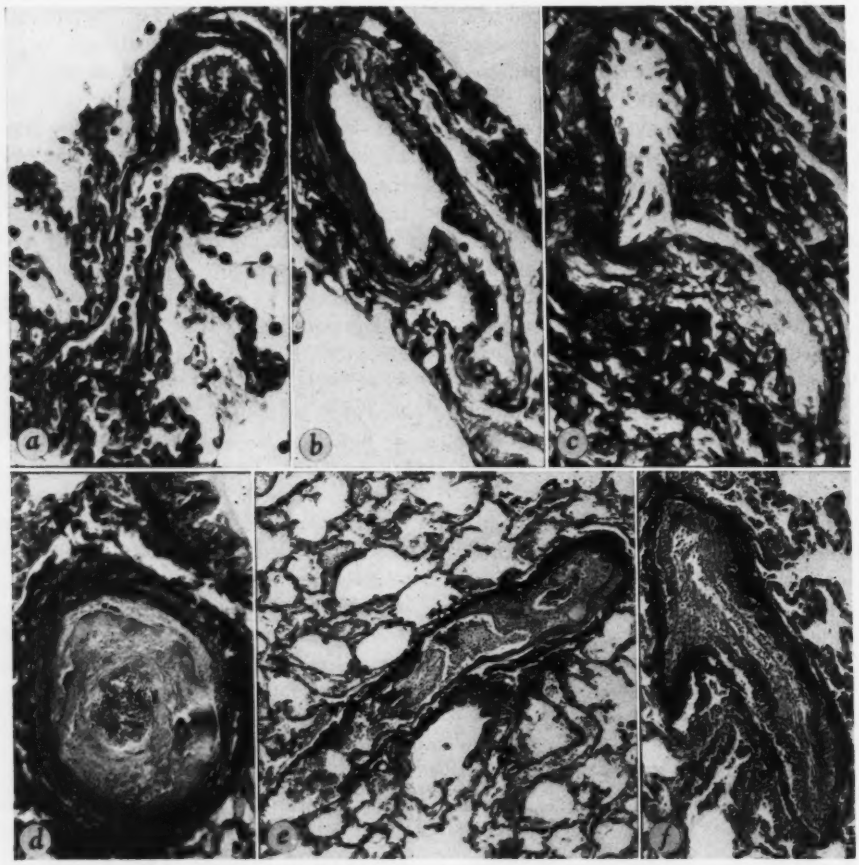

FIG. 5. *a*. Pulmonary small muscular artery and arteriolar branch in a 5-year-old patient with a small ventricular septal defect. The wall is thin and the lumen is wide (ELVG; reduced from × 330). *b*. Small muscular artery and arteriolar branch from an 8-month-old infant with a large ventricular septal defect and pulmonary hypertension. Medial hypertrophy (ELVG; reduced from × 330). *c*. Small muscular artery and arteriolar branch from a 6-year-old child with multiple large ventricular septal defects. Medial hypertrophy. A suggestion of intimal fibrous thickening at origin of arteriole (ELVG; reduced from × 330). In patients represented in *b* and *c* the pulmonary bed was designated as of the high resistance-high reserve type. *d* and *e*. Large muscular arterial lesions in a 6½-year-old child with a large ventricular septal defect and the high resistance-low reserve type of pulmonary vasculature. *d*. Marked intimal narrowing by hyalinized connective tissue (ELVG; reduced from × 200). *e*. Longitudinal section of artery showing focal intimal thickening with hyalinized and cellular connective tissue yielding a narrow and irregular lumen. There is thinning of the arterial wall distal to the intimal lesions (ELVG; reduced from × 50). *f*. A small muscular artery from a 6½-year-old child with a large ventricular septal defect and patent ductus arteriosus; a high resistance-low reserve pulmonary tree. Intimal fibrous thickening (ELVG; reduced from × 100).

The characteristic lesion is not an organized thrombus in our opinion, although in the same case organized thrombosis may also exist. The intimal arterial lesions which may be seen in ventricular septal defect are also observed in some cases of patent ductus arteriosus, atrial septal defect and so-called primary pulmonary hypertension. These lesions have been the subject of considerable interest in the literature.[64] Some have claimed them to be glomuslike congenital malformations.

Others have suggested that these lesions

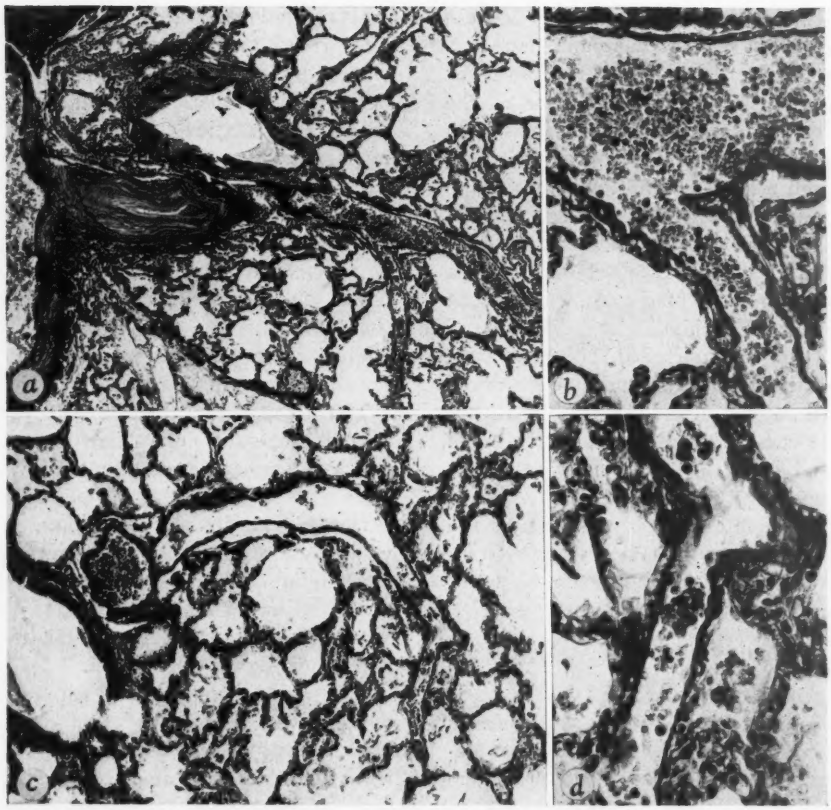

FIG. 6. From the case illustrated in figure 5*d* and *e* of a 6½-year-old child with a large ventricular septal defect and a high resistance-low reserve type of pulmonary vasculature. *a*. A large muscular artery shows intimal narrowing with hyalinized connective tissue. A thin-walled vessel beyond (to the right) was shown on serial section to arise from the occluded vessel (ELVG; reduced from × 45). *b*. High-power view of an arteriole arising from the thin-walled segment of artery illustrated in *a* (hematoxylin and eosin; reduced from × 200). *c*. An artery and an arteriole not associated with intimal occlusion of the parent artery. The lumina are wide and the walls are thin (ELVG; reduced from × 90). *d*. High-power magnification of the arteriole arising from the thin-walled artery illustrated in *c* (ELVG; reduced from × 330).

are arteriovenous communications.[65-67] This implies that cyanosis, which may appear in ventricular septal defect, is a consequence of a shunt through these hypothesized channels. Neither of these claims can be supported, since the lesions may readily be demonstrated by serial sections to be confined to arteries.[54, 64, 68-72] Additional support comes from physiologic studies in patients with ventricular septal defect who have such arterial lesions. When dye-dilution curves are compared following injection of dye into the right ventricle and into the pulmonary trunk, it becomes readily apparent that the injection into the right ventricle is associated with a right-to-left shunt, while the injection into the pulmonary trunk shows no evidence of a right-to-left shunt. This evidence therefore does not support the presence of an arteriovenous shunt in the lung, nor does it support any other claim that the cyanosis in patients with ventricular septal defect is of pulmonary origin. The evidence, as well as the observation of fully saturated blood in the left atrium,[73] establishes that the desaturation of the systemic arterial blood is derived from a shunt through the ventricular

septal defect rather than pulmonary vessels.

The lung that has the anatomic characteristic that I have called "high resistance-low reserve" has a remarkable difference at the level of the small arteries and arterioles when compared to the lung classified as "high resistance-high reserve" (fig. 6). Whereas in the latter the arteries and arterioles show medial hypertrophy with correspondingly narrow lumina, most of the small vessels of the high resistance-low reserve lung show wide lumina and thin walls. The thinning and dilatation of the vessel wall are universal, occurring both beyond obstructed arteries and in areas where arteries are not obstructed.

In some cases, the dilatation of the small arteries and of the arterioles may reach extreme proportions with aneurysmlike formation. Where these dilated vessels lie near the air spaces, they may herniate into them. Rupture may perhaps be the basis for hemoptysis, which occurs in patients with this type of pulmonary vascular bed.[54, 74]

Brewer[71] has indicated that some of these dilated vessels represent collateral channels arising from pulmonary arteries above the sites of obstructed lumina to the vascular bed beyond. Heath[74] has suggested that some are collateral channels from the bronchial arterial system. The majority of the dilated vessels have normal sites of origin and termination.

The location of the intimal occlusive lesions in relatively large arteries correlates well with observations in postmortem angiographic studies, where the arteries show a blunted configuration.[75, 76] This has been called a "pruning" effect by Evans.[68] In addition to the intimal lesions of large muscular arteries, necrosis and thrombosis may be observed in similar vessels.[77-82]

The pulmonary vascular bed with occlusive intimal arterial lesions always displays a high resistance to flow. What then is the explanation for the apparent paradox of a high resistance to flow in the presence of dilated small arteries and arterioles?

The occluded arteries are large ones, often being 0.3 mm. or wider in diameter, and therefore are the channel for the blood supply to a relatively large area of pulmonary tissue. With multiple lesions of this type, a considerable amount of the pulmonary vascular bed is eliminated from the effective perfusion channel of the lesser circulation, even allowing for some collateral circulation to this area from the pulmonary arteries. As far as the functional capacity of the pulmonary vascular bed is concerned, it is as though portions of the lung had been extirpated (fig. 7*a*). Ferguson and Varco[83] have removed portions of the lung and produced pulmonary hypertension by reducing the total capacity of the vascular bed and additionally by increasing the flow to the remaining pulmonary tissue.

The atrophy and dilatation of the vessels beyond areas of obstruction are a feature which is similar to that in small vessels in cases with obstruction at the major pulmonary pathway. The atrophy and dilatation in the vessels not associated with obstructed arteries seem to be a response on the part of the effective portion of the pulmonary circuit to accommodate as much blood as is possible in this remaining functional area.

It is of significance that in spite of this compensatory mechanism, however it is brought about, the total capacity of the effective pulmonary bed is so limited that a high pulmonary vascular resistance exists. This type of pulmonary vascular bed may be said to have reached the limits of its capacity to receive blood from the right ventricle, even though the vessels participating individually are wide-lumened and thin-walled.

The intimal lesions of large muscular arteries, in our opinion, are specific for pulmonary hypertension of a severe degree and of chronic nature. We have not observed them in other circumstances.

In addition to the 2 clear-cut types of pulmonary vascular beds that are usually encountered among patients with ventricular septal defect (fig. 7*a*), there is an occasional case that presents a transitional type of pattern (fig. 7*b* and *c*). In this, a few small arteries, usually about 100 microns or less in diameter, are occluded by intimal fibrous tissue. The unoccluded small arteries and the arterioles show a wall-thickness that is either normal or slightly greater than normal, while the lumina are of

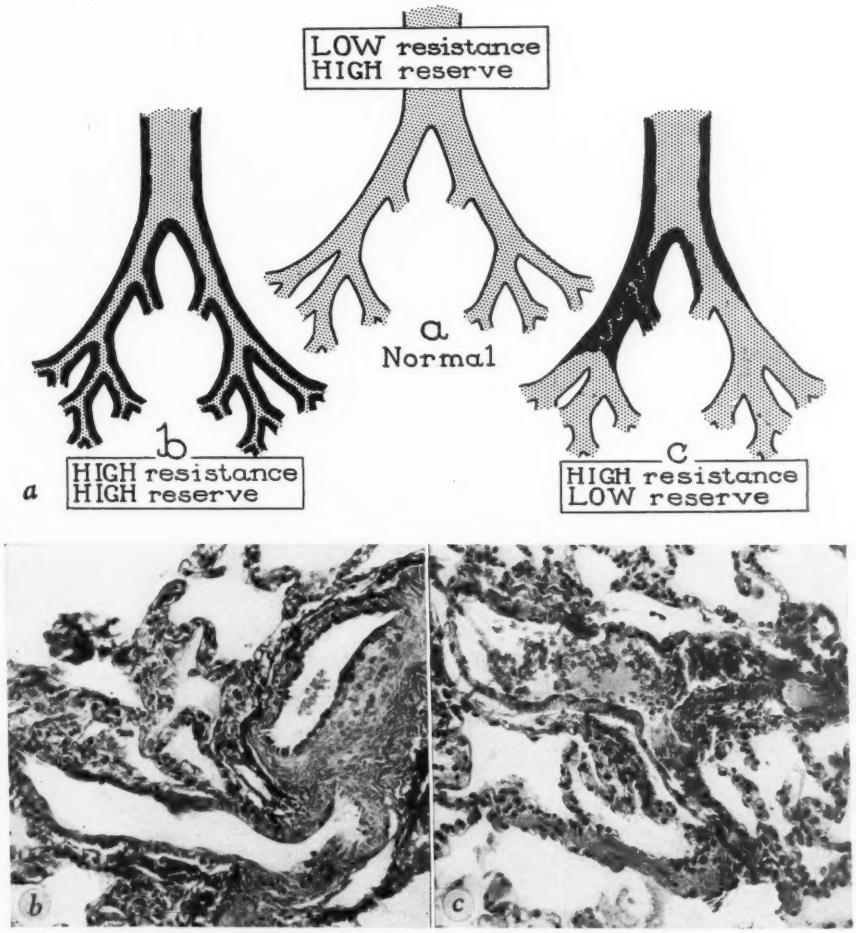

FIG. 7. *a*. Diagrammatic representation of the normal pulmonary arterial system and that in the 2 basic types with a free communication between the ventricles or great arteries. *b* and *c*. Photomicrographs of pulmonary vessels from a 6-year-old girl patient with a patent ductus arteriosus and pulmonary hypertension, showing a transitional type of pulmonary vascular tree. *b*. The 2 vascular channels were shown by serial section to communicate through a zone of intimal narrowing at the origin of the small arterial branch (ELVG; reduced from × 200). *c*. An artery and an arteriolar branch not related to intimal fibrous thickening, showing essentially a normal structure (hematoxylin and eosin; reduced from × 200).

normal width. There is lacking the element of excessive width of small vessels seen in cases with intimal occlusion of larger arteries. In the transitional forms the large muscular arteries have medial layers thicker than normal.

Correlation of Functional Features with Structural Changes in the Pulmonary Vascular Bed. That there are 2 basic types of pulmonary vascular patterns in patients with ventricular septal defect is of very great importance for practical reasons. In one type closure of the defect may yield essentially normal pulmonary pressure, while in the other type closure of the defect is associated with retention of pulmonary hypertension. In fact, with the defect closed, the pulmonary arterial pressure may even rise above aortic pressure.

Cases known to have the high resistance-

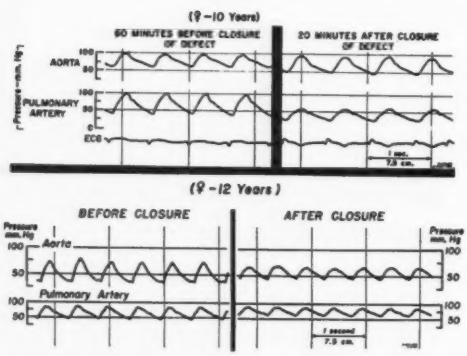

FIG. 8. Preoperative and postoperative pressure studies in 2 patients with ventricular septal defect. In the 10-year-old girl the pulmonary vascular pattern was of the high resistance-high reserve type. The heart and preoperative dye-dilution curves of this patient are illustrated in the left-hand column of figure 3. In the 12-year-old girl the pulmonary vascular pattern was of the high resistance-low reserve type. Illustrations of the pulmonary vessels from this case appear in figure 5*d* and *e* and in figure 6. The defects were closed by Dr. J. W. Kirklin.

high reserve type of pulmonary vascular bed show a lowering of pulmonary pressure after closure of the defect (fig. 8). This may simply reflect the reduction in pulmonary flow without change in resistance. It does not necessarily mean that the fall in pulmonary pressure is an expression of fall of pulmonary resistance. While it is expected that such would occur in this type of patient after the defect is closed, the pulmonary resistance need not be expected to fall immediately with the surgically created change in circulation. From the demonstration of a gradual rather than abrupt fall in pulmonary vascular resistance after surgical relief of mitral stenosis one would expect that in ventricular septal defect a postoperative fall in pulmonary resistance would also be gradual. The demonstration of a fall in pulmonary vascular resistance after closure of the defect is yet to be accomplished and will require cases in which complete physiologic studies preoperatively and postoperatively have been done.

Among cases known to have the high resistance-low reserve type of pulmonary vascular bed the pulmonary pressure may rise or remain constant after closure of the defect. When it rises, the reason is probably best explained as follows. Before closure of the defect and in the face of a very high pulmonary vascular resistance, the defect operated as an "escape valve" allowing a right-to-left shunt of that volume of blood in excess of that which caused pulmonary pressure to be at systemic levels. With closure of the escape valve, no shunt is possible and all the right ventricular blood is ejected into the pulmonary vascular bed. The volume of pulmonary flow is now greater than when a right-to-left shunt existed. In the presence of a fixed pulmonary vascular resistance the increased pulmonary flow yields increased pulmonary arterial and right ventricular pressures. If this becomes sufficiently high the right ventricle may fail abruptly in the postoperative period.

With this difference in behavior among cases it is important to predict, if possible, which type of vascular tree is present before surgical treatment is recommended. For this reason it was pertinent to see whether functional studies could indicate the anatomic type of vascular bed present.

In 15 cases having large ventricular septal defect, a single ventricle without stenosis or patent ductus arteriosus with pulmonary hypertension in which serial sections of lungs had been examined there were available physiologic studies that yielded figures for pulmonary and systemic flows when the patients breathed air and 100 per cent oxygen. From these figures, values for total systemic and total pulmonary resistance could be calculated under these 2 conditions. Dr. H. F. Helmholz, Jr., reviewed the physiologic data independently of the observations on structural changes and then the two were correlated[84] in an attempt to see whether the structural type of pulmonary vascular tree could be predicted from the hemodynamic characteristics.

The most reliable basis for prediction, as judged by this material, is to know the ratio of total pulmonary resistance to total systemic resistance when the patient breathed air and when he breathed 100 per cent oxygen.

In a flexible pulmonary vascular bed total pulmonary resistance falls when the inspired gas has a greater oxygen content than air. This is true not only in the normal but also in certain patients with congenital cardiac disease.[85]

The cases were divided according to the 3

structural types of pulmonary vascular bed already described.

The results are illustrated in figure 9.

The high resistance-high reserve and transitional types of vascular beds were associated with varying ratios of total pulmonary and total systemic resistance when the patient breathed air but in no case was the ratio more than 0.7:1. That is, though the pulmonary resistance might be elevated, it did not exceed total systemic resistance. In each of these 2 types of vascular beds with breathing of 100 per cent oxygen there was a significant fall in pulmonary resistance compared to systemic, so that in no case was the ratio greater than 0.4:1 under these circumstances.

In contrast, when the patients with the high resistance-low reserve type of pulmonary vascular bed breathed air the total pulmonary resistance approached, equaled or exceeded the systemic resistance.

When 100 per cent oxygen was administered to this group, there was usually a slight fall in pulmonary resistance compared to systemic, but in no case that we observed did it fall below a ratio of 0.6:1. In some cases the ratio did not differ much from 1:1.

These observations indicate that from hemodynamic data there is possible a rough separation between the cases having the high resistance-high reserve or transitional types of pulmonary vascular beds on one hand and the high resistance-low reserve bed on the other, even when the patient breathes air. The distinction becomes much more evident when 100 per cent oxygen is administered.

It is probable that biopsy of a chance section of the lung might yield a high degree of accuracy as to the structural type of pattern. The type with only medial changes is simple to identify. In the types with intimal arterial lesions there is no certainty that a biopsy would necessarily yield a characteristically occluded vessel. The finding of prominently dilated small vessels in a patient with known high resistance to pulmonary flow would be strong evidence favoring the presence of intimal arterial lesions even if these were not present in the particular piece of tissue.

The question naturally arises as to the relationship between the 3 types of vascular trees.

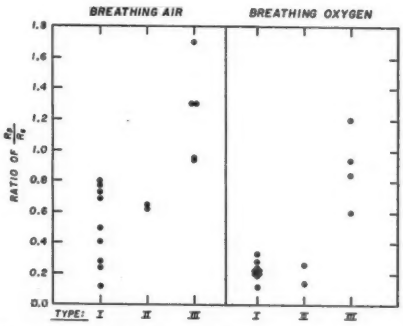

FIG. 9. Ratios of total pulmonary to total systemic vascular resistance among 15 patients with a free communication between the ventricles or great arteries. A sixteenth case with a ratio of 0.9:1 on air did not have studies on oxygen. Type I refers to a high resistance-high reserve pulmonary vascular bed, type II to a transitional form, and type III to a high resistance-low reserve pulmonary vascular tree.

Our opinion is that the high resistance-high reserve type of bed is essentially an integral part of the anatomicofunctional complex of a congenital unobstructed communication between the ventricles without pulmonary stenosis. We believe this to be the type of lung with which such patients are born. The medial hypertrophy does not represent a malformation, but rather we believe that it represents a persistence of a fetal type of pulmonary vessel, just as in the over-all function of the heart with the defect there is carried over from the fetal into the postnatal state a free communication between the 2 circulations.

The transitional and high resistance-low reserve types of vascular tree, in our opinion, are complications of long-standing pulmonary hypertension in which the pulmonary systolic pressure equals or approaches systemic systolic pressure. That one type gives way to the other is supported by different age patterns between the cases without intimal arterial lesions on one hand and those with such lesions on the other. Among patients with a free communication between the ventricles or great arteries we have observed only the high resistance-high reserve type of bed among patients less than 2 years of age. This type of pattern persists for varying lengths of time. We have observed it in patients aged 10 and 37 years respectively, but the last case is most unusual. In general, the older the patient, the more likely he is to have 1 of the other 2 types of

pattern. While occasional patients as young as 2 years may show the transitional or the high resistance-low reserve type, the high resistance-low reserve pattern is usually present in patients who have carried a defect of the type under discussion for 20 or more years. It is only the exceptional patient who does not.

Ventricular Septal Defect with Pulmonary Stenosis

We have just completed the description of ventricular septal defect without pulmonary stenosis. In this discussion it was brought out that while the aortic ostium is in free communication with both ventricles, the nature and direction of shunts depend principally on relative resistances to the flow of blood through the 2 circulations. When a high resistance to pulmonary flow exists, the basis for this resides in changes within the pulmonary arterioles and arteries. In some instances of ventricular septal defect without pulmonary stenosis, the resistance to pulmonary flow may be greater than the resistance to systemic flow. This results in a right-to-left shunt. The same functional derangements as in ventricular septal defect without pulmonary stenosis may occur in a condition that in the past has been considered quite a separate one from ventricular septal defect without pulmonary stenosis. This is the so-called tetralogy of Fallot, characterized anatomically by biventricular origin of the aorta above a large ventricular septal defect, right ventricular hypertrophy, and stenosis of the major pulmonary pathway. In the past, it was thought that this condition was always associated with a significant right-to-left shunt and with cyanosis. Recent experiences have shown that among patients with basically the same anatomic complex of malformations, there is a spectrum of functional changes essentially identical with that in ventricular septal defect without stenosis.[86-88] The reason for the similarity in spectra between the 2 conditions resides in the fact that in the so-called tetralogy of Fallot, there are varying degrees of pulmonary stenosis.

The range in behavior among patients having anatomically the tetralogy of Fallot is well illustrated by 3 cases with varying degrees of pulmonary stenosis shown in figure 10. In the first instance, the degree of pulmonary stenosis was mild. The pulmonary arterial pressure, though lower than the right ventricular pressure, was still elevated above normal. There was only a left-to-right shunt and no right-to-left shunt.

Histologically, the pulmonary vessels showed medial hypertrophy of the arteries and arterioles indistinguishable from that seen in cases of large ventricular septal defect without pulmonary stenosis.

We may recall the concept that, when a ventricular septal defect is present, the left ventricle is functionally in communication with the pulmonary arteries. The pulmonary stenosis represents an obstruction in that communication. In the case with the mild pulmonary stenosis, the obstruction was so mild that it did not represent an effective barrier between the left ventricle and the pulmonary vessels, as evidenced by the elevated pulmonary arterial pressure. This mild obstruction represented 1 focus of increased resistance to pulmonary flow, but was ineffective in controlling the amount of blood flowing through the lungs. A second zone of increased resistance to pulmonary flow lay in the small vessels of the lung, just as in large ventricular septal defect without pulmonary stenosis.

In the second case, the pulmonary stenosis was of moderate degree, and the pulmonary arterial pressure was essentially normal. Functionally, a small right-to-left shunt and a larger left-to-right shunt were demonstrated. Histologically, the pulmonary vessels were normal. Here, the pulmonary stenosis was an effective barrier between the left ventricle and the pulmonary arteries, and it was the main controlling factor in the volume of flow to the lungs. The small pulmonary vessels are thus relieved of the responsibility of being a governing factor controlling blood flow to the lungs.

Realizing the fact that this patient had a large ventricular septal defect, the pulmonary stenosis here was of a degree that might be termed ideal. While allowing sufficient pulmo-

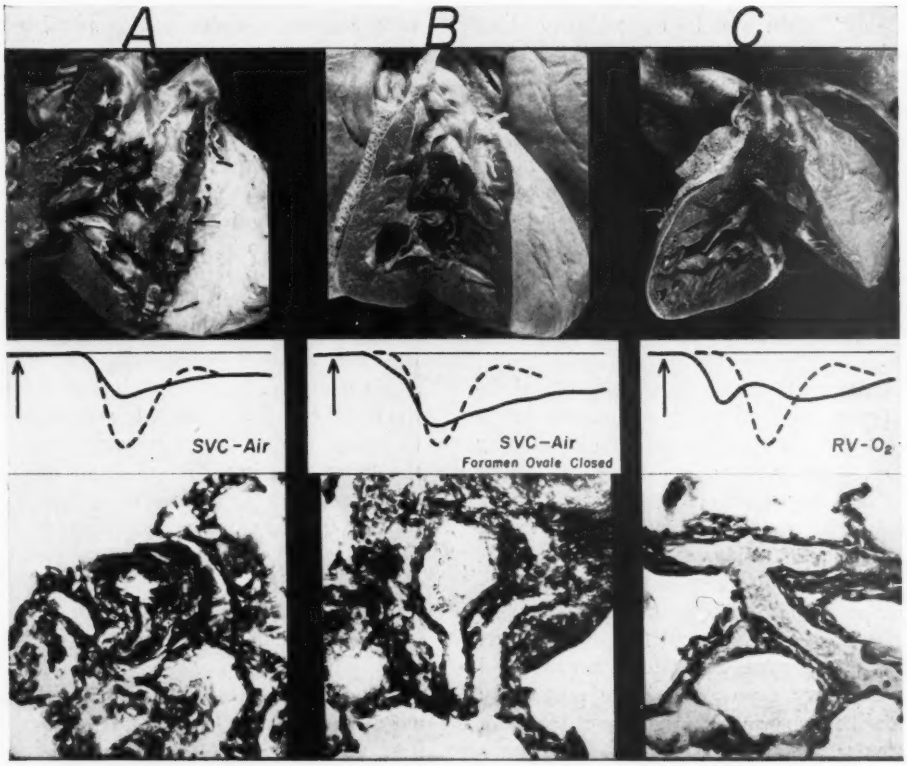

FIG. 10. The outflow tract of the right ventricle, preoperative dye-dilution curves (solid curves for particular cases; dotted curves for anticipated normal) and the small arteries with arteriolar branches in three cases of ventricular septal defect with infundibular stenosis of varying degrees. In each case the ventricular septal defect had been closed and infundibular resection had been performed at operation (see text for contrasting features among the cases).

nary flow it removed from the small pulmonary vessels the responsibility of governing volume of pulmonary flow and did not allow them to be subjected to high levels of pressure, with the attendant complications. At the same time, while the pulmonary vessels were effectively protected from the ventricular pressure, the right-to-left shunt caused by the pulmonary stenosis still was only of minor magnitude. Such an ideal arrangement is the one sought in the procedure of creating pulmonary stenosis in patients with ventricular septal defect in whom closure of the ventricular septal defect is not attempted.[13]

In the third case, the pulmonary stenosis was so severe that a large right-to-left shunt resulted, making the patient cyanotic. Here we have the traditional picture of the tetralogy of Fallot with so high a degree of resistance to pulmonary flow at the right ventricular outflow tract as to exceed systemic resistance. Here then, the shunt was predominantly right-to-left. The pulmonary vessels were normal or thinner than normal. Thus while in the first case the pulmonary vessels were insufficiently protected, in the third case the pulmonary vessels were effectively protected from ventricular pressure but only at the expense of a right-to-left shunt.

I have indicated that the term "Eisenmenger complex" might with advantage be replaced by a descriptive term indicating the characteristics of the hemodynamic derangement. Likewise, it is evident that the term "tetralogy

of Fallot" might also be conveniently abandoned.

Because the functional derangement of patients with basically the same anatomic defect is so varied, it seems more appropriate to identify cases by such functionally descriptive terms as, for example, "ventricular septal defect with mild pulmonary stenosis and left-to-right shunt," "ventricular septal defect with moderate pulmonary stenosis and bidirectional shunts" or "ventricular septal defect with severe pulmonary stenosis and right-to-left shunt."

If we recall that in a ventricular septal defect there is functionally a communication between the left ventricle and the pulmonary arteries, then we recognize certain similarities in the behavior of this communication among patients with small ventricular septal defect without pulmonary stenosis, on the one hand, and patients with large ventricular septal defects and significant degrees of pulmonary stenosis, on the other hand. In each instance, there is a barrier between the left ventricle and the pulmonary arteries, and the pulmonary vascular bed is normal. In the case of the small ventricular septal defect without pulmonary stenosis, the barrier in the communication lies at the small obstructing ventricular septal defect. In the case of large ventricular septal defect with severe pulmonary stenosis, the obstruction between the left ventricle and the pulmonary arteries is at the site of pulmonary stenosis.

Functional Single Ventricle

In cases of single ventricle, whether this represents a single ventricle anatomically or only functionally, the basic dynamics are essentially like those in ventricular septal defect. Two major subgroups exist, namely, single functioning ventricle without pulmonary stenosis and single functioning ventricle with pulmonary stenosis. In the cases of single functioning ventricle without pulmonary stenosis, the pulmonary and systemic pressures are essentially equal and the regulation of distribution of blood flow to the systemic circulation, on one hand, and to the pulmonary circulation, on the other, is dependent on relative resistances in the two circulations.

Assuming that the systemic resistances are at normal levels, which is usually the case, the variable factor is the pulmonary resistance, exactly as in large ventricular septal defect. Cases with functional single ventricle without pulmonary stenosis show the same range of vascular changes in the lung as in large ventricular septal defect.[74, 80] While theoretically there is a tendency for free mixing of blood in the same ventricle, this has not proved to be the case, at least in regard to the anatomic single ventricle. Here there is a tendency for the blood entering through the tricuspid valve to stream toward the pulmonary trunk, while the blood entering through the mitral valve streams toward the aorta. Under these circumstances, the pulmonary arterial oxygen saturation is lower than that of the systemic arterial circulation. Even with functional studies, it may be impossible to distinguish the single ventricle without pulmonary stenosis from a large ventricular septal defect.[89]

Just as the single ventricle without pulmonary stenosis may be difficult to distinguish from ventricular septal defect without pulmonary stenosis, so the single ventricle with pulmonary stenosis may not be readily distinguished from ventricular septal defect with pulmonary stenosis.

In cases in which the single ventricle is associated with pulmonary stenosis, the governing factor in distribution of blood is the zone of obstruction leading to the pulmonary trunk. Usually, the resistance to flow through this is so high that the greater proportion of blood leaving the common ventricle enters the aorta and there is therefore a significant right-to-left shunt.

When the common ventricle is associated with significant pulmonary stenosis, the pulmonary vessels are in the range of normal structurally.

Patent Ductus Arteriosus

The dynamics in patent ductus arteriosus are very closely related to those in ventricular septal defect. Were there significant resistance to flow through the ductus arteriosus during

fetal life, the right ventricular pressure would have to exceed the left ventricular pressure in order for blood to enter the descending aorta through the ductus.

We know that the pressure in the 2 ventricles is essentially equal, and we must therefore conclude that in the fetus the ductus arteriosus does not constitute an obstructed channel. It may be said therefore to allow free communication between the aorta and the pulmonary arteries.

In the patient who is destined to postnatal persistent patency of the ductus arteriosus, it is not known whether at birth the functional occlusion of the ductus thought to be present in the normal is also present here. It is possible that, in the patient who is to have persistent patency of the ductus, the ductus does act normally at the time of birth. Subsequent to birth, however, persistent patency of the ductus arteriosus results from failure of growth of the structural elements of the media and intima of the ductus which normally close the ductus. The persistently patent ductus seems simply to have maintained the same structure that it had in the normal before birth.

Recognizing that during fetal life the ductus is a nonobstructing channel of all individuals, one may assume that it is a similar channel in the neonatal period of individuals who are to maintain patency of the ductus. This means that the arterial sides of the lesser and greater circulations are in free communication at this time. From this we may imply that in all patients with persistent patency of the ductus arteriosus, there is a phase of pulmonary hypertension in which the pulmonary and systemic arterial pressures are about equal. The absence of a continuous murmur in most infants with patent ductus arteriosus may thus be due to equivalent pressures in both circulations.[90, 91] In later life, patients with patent ductus arteriosus can readily be separated into 2 major groups, comparable to patients with small and with large ventricular septal defects. The majority of patients with patent ductus arteriosus have an arrangement which is like that of patients with small ventricular septal defects in that the ductus represents an obstructing communication between the left ventricle and the pulmonary arteries. A differential in pressure exists between the left ventricle and aorta on one hand, and the pulmonary arteries on the other. In cases of this type, the pulmonary vascular bed is protected from the pressure in the left ventricle and systemic circulation by the obstructive type of ductus arteriosus. The small pulmonary vessels are normal.[16]

The second type is the one in which the ductus arteriosus is so short and wide that there is no significant pressure difference across it. These cases may therefore be compared with the large ventricular septal defect. In them, the systemic and pulmonary arterial pressures are in the same general range. The regulation of the volume and direction of shunt depend primarily on the relation of the systemic to the pulmonary resistances. The pulmonary resistance is usually higher than normal.

The pulmonary vascular changes are like those in large ventricular septal defect. One may be termed the high resistance-high reserve type of vascular tree; the other, the high resistance-low reserve vascular tree. As in ventricular septal defect, transitional forms between the two exist.

Let us return to the fact that in children and adults 2 types of ductus arteriosus are present, while in the neonatal period it is hypothesized that all patients with patent ductus arteriosus have pulmonary hypertension. What is the basis for persistence of pulmonary hypertension in one group and its disappearance in the other? The basis for this seems to lie in a different type of resistance to flow through the ductus, high in one and low in the other.

In the patient who develops a high resistance to flow through the ductus, a possible explanation is that, as the patient grows, there is a differential quality to the growth. That is, the aorta and the pulmonary artery may grow in diameter out of proportion to that of the patent ductus. The relatively narrow state of the ductus constitutes an obstruction to flow and permits a pressure differential to exist across the ductus, a feature which is characteristic of the so-called classic patent ductus arteriosus.

In the second group, the orifice of the ductus

arteriosus seems to grow in concert with the diameters of the aorta and pulmonary trunk. This short and wide type of ductus represents a nonobstructive opening allowing equivalent pressures in the aorta and the pulmonary arteries.[92]

Atrial Septal Defect

For purposes of discussion, patients with atrial septal defect may be divided into 2 age groups, (1) infants and children, and (2) adults. Adults may be further subdivided into those with low pulmonary vascular resistance and normal pulmonary pressures and those with elevated pulmonary vascular resistance and pressures.

The story as regards infants and children still has many unsettled points. In adults the situation is clearer. We shall first discuss the adult with atrial septal defect.

Adult Patients

Low Pulmonary Vascular Resistance and Normal Pulmonary Pressure. In atrial septal defect with low pulmonary vascular resistance and normal pressure and high pulmonary flow as determined by functional studies, the structural nature of the pulmonary vascular tree is that of a low-pressure system. Throughout the arterial system, including the arterioles, the lumina are wide and the walls thin (fig. 11*a* and *b*). Anatomically, the system cannot be distinguished with certainty from normal, but the tortuosity of the arteries not seen in the normal suggests a high flow.

Elevated Pulmonary Vascular Resistance and Pressure. There is a tendency for patients with ordinary atrial septal defect to develop, gradually, an increasing pulmonary vascular resistance and pulmonary hypertension while retaining for a time, at least, a high pulmonary flow. This tendency is apparent in patients reaching the fourth decade of life, although there are exceptions both ways: younger adult patients may manifest pulmonary hypertension while some older patients delay or never show, within the period of study, a tendency for elevating pulmonary vascular resistance and pressure.

Adult patients who have an increased pulmonary vascular resistance and increased pulmonary arterial pressure may conveniently be divided into 2 groups. In the first group the pulmonary pressures are below those in the systemic arteries. Among these patients, pulmonary arterial systolic pressures from 40 to 80 mm. of mercury are frequently encountered. This group may be said to have moderate pulmonary hypertension. In the second group the pulmonary arterial pressures are in the range of aortic pressures, although not necessarily identical. The pulmonary pressure may even exceed the aortic. This group may be said to have severe pulmonary hypertension.

The foregoing 2 groups of patients with elevated pulmonary arterial pressures are separated, not because they are basically different, but because 1 group, the first, seems to represent an earlier and lesser degree of a complication of atrial septal defect than the latter.

There are different anatomic pictures in the pulmonary vascular tree in these 2 groups of patients with elevated pulmonary arterial pressures, the 2 anatomic types functionally representing different degrees of elevated pulmonary vascular resistance.

Moderate Pulmonary Hypertension. The patients with moderate pulmonary hypertension show a widely varying pattern in the small muscular arteries and arterioles, ranging from completely occluded vessels to very thin-walled, abnormally wide ones (fig. 11*c*, *d*, *e*, and *f*).

The large muscular pulmonary arteries show medial hypertrophy, a feature that closely reflects the degree of pulmonary arterial and right ventricular pressures.

Significant occlusive lesions in the form of cellular fibrous intimal thickening are seen in the small arteries and at the beginnings of arterioles. With serial sections, it is readily demonstrated that these lesions are focal.

For example, as one traces an occluded arteriole distally, the lumen eventually opens up and the vessel is wide. It is obvious that, were the distal unobstructed part of such a vessel examined in a chance single section, one would falsely gain the impression that it was

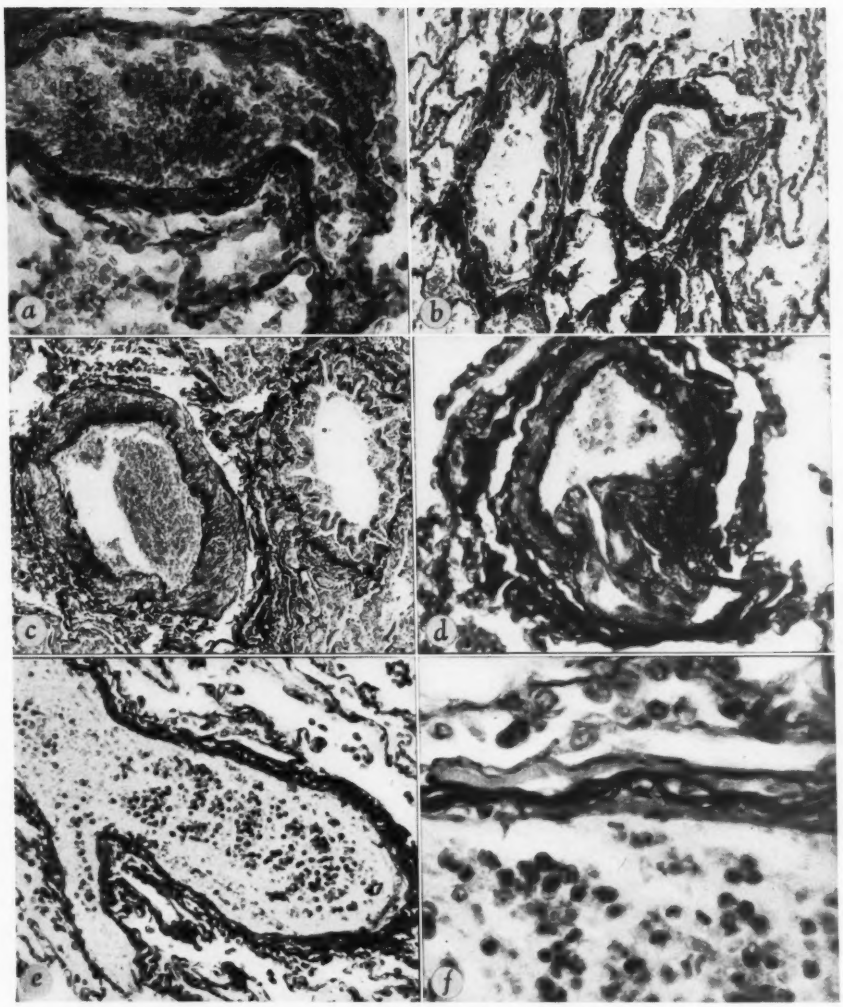

FIG. 11. Photomicrographs of pulmonary vessels in adult patients with atrial septal defect. *a* and *b*. From a 41-year-old woman with high pulmonary flow and normal pulmonary arterial pressures. *a*. Small muscular artery and arteriolar branch, showing thin walls and wide lumina (ELVG; reduced from × 330). *b*. A large muscular artery and a bronchiole. The arterial wall is thin and the lumen is wide, features not distinguishable from the normal (ELVG; reduced from × 70). *c*. From a 46-year-old patient with left-to-right shunt and moderate pulmonary hypertension (pulmonary arterial pressure 89/20 to 100/37). Medial hypertrophy of the large muscular artery, which lies beside a bronchiole (ELVG; reduced from × 70). *d*, *e*, and *f*. From a 34-year-old patient with moderate pulmonary hypertension. *d*. A small muscular artery and an arteriolar branch. Medial hypertrophy of the artery, intimal occlusion by fibrous tissue of the arteriolar origin (ELVG; reduced from × 330). *e*. A small muscular artery and an arteriolar branch not related to occlusive intimal lesions, showing exceedingly wide lumina (reduced from × 200). The wall of the artery is atrophic, as illustrated in *f*. *f*. Detail of wall in dilated artery shown in *e*. The medial muscle is almost entirely absent, the wall now being represented by the condensation of the 2 elastic laminae and fibrous thickening of the intima and adventitia (ELVG; reduced from × 570).

an unobstructed vessel, when in reality it is completely closed more proximally. When the complication of intimal small arterial and arteriolar occlusion develops, the extensiveness of its distribution can therefore never be fully appreciated from individual histologic sections, regardless of how many sections are taken.

The intimal lesions at arteriolar level lie in thin-walled vessels. Some small arteries with intimal occlusive lesions show thin media, while in some this layer is hypertrophied. Why is there this difference? The answer may perhaps be found in the large muscular arteries. These vessels in patients having atrial septal defect and no pulmonary hypertension are thin, in the range of normal. Yet when pulmonary hypertension develops, they become thickly muscular. They accompany the myocardium with regard to hypertrophy and in their hypertrophy the large muscular arteries reflect the level of pressure within them. With regard to the varying picture in the media of the small arteries that have intimal occlusive lesions, it may be postulated that in the thick ones obstruction existed more peripherally and that elevation of arterial pressure existed before the small artery itself developed intimal lesions. By the same reasoning, those arteries with thin mediae and occluding intimal lesions developed the intimal lesions early, before significant elevation of pressure had occurred.

This leads us to a consideration of the nonobstructed small arteries and arterioles among the patients with moderate pulmonary hypertension.

These show unusually wide lumina and often atrophic mediae. The arterial walls may no longer have identifiable muscle, being composed principally of the elastic membranes and varying amounts of collagen. Frequently, there is a thick, uniformly deposited layer of acellular collagen in the intima. The latter type of change may be seen in normal control patients of comparable age, but the number of vessels involved in the normal is far less than in patients with atrial septal defect.

What is the functional significance of the structural changes encountered in the patients with moderate pulmonary hypertension and elevated pulmonary vascular resistance?

While the development of medial hypertrophy of the larger muscular arteries may be a contributing factor to elevated resistance, the intimal lesions of the small arteries and arterioles are most peripherally located and seem to be the initiating factor in elevating the pulmonary vascular resistance. Recognizing that the intimal lesions of the smallest arterial vessels are characteristic of the patients with moderate or only slightly elevated levels of arteriolar resistance, they cannot be charged to elevated pressure. These intimal lesions seem properly to be credited to the factor of high flow. The turbulence and abnormal vibrations that are probably set up in these small vessels as great volumes of blood flow through them may represent mechanical irritation. The intimal cellular fibrous response may be in the category of a reparative reaction.

Although elevation of total pulmonary resistance results from the occlusion of many small arteries and arterioles, a high flow characteristically continues through the lungs and with this combination of circumstances there is an elevation of pulmonary arterial pressure. This factor is probably responsible for distention of the unoccluded small vessels—being the ones through which the pulmonary blood must inevitably flow. Whether such a process of distention causes simply atrophy or causes disruption in the normal attachments of the medial smooth muscle fibers, and secondarily atrophy, is not known. What is known, as has been indicated, is that many of the unobstructed small arterial vessels are devoid of distinct muscle layers. The connective tissue, including the elastic tissue of the vessel, represents the only remaining significant element that maintains the integrity of the vessel. It is realized, however, that a vessel so altered may offer little, if any, active constriction, now being simply a passive structure with a wide lumen and a connective-tissue wall.

It is demonstrable, however, that in a patient with such elements in the pulmonary vascular tree, there still remains a vasoconstrictive function. Perhaps this is brought about by action of the hypertrophied media of the large muscular arteries, for structurally,

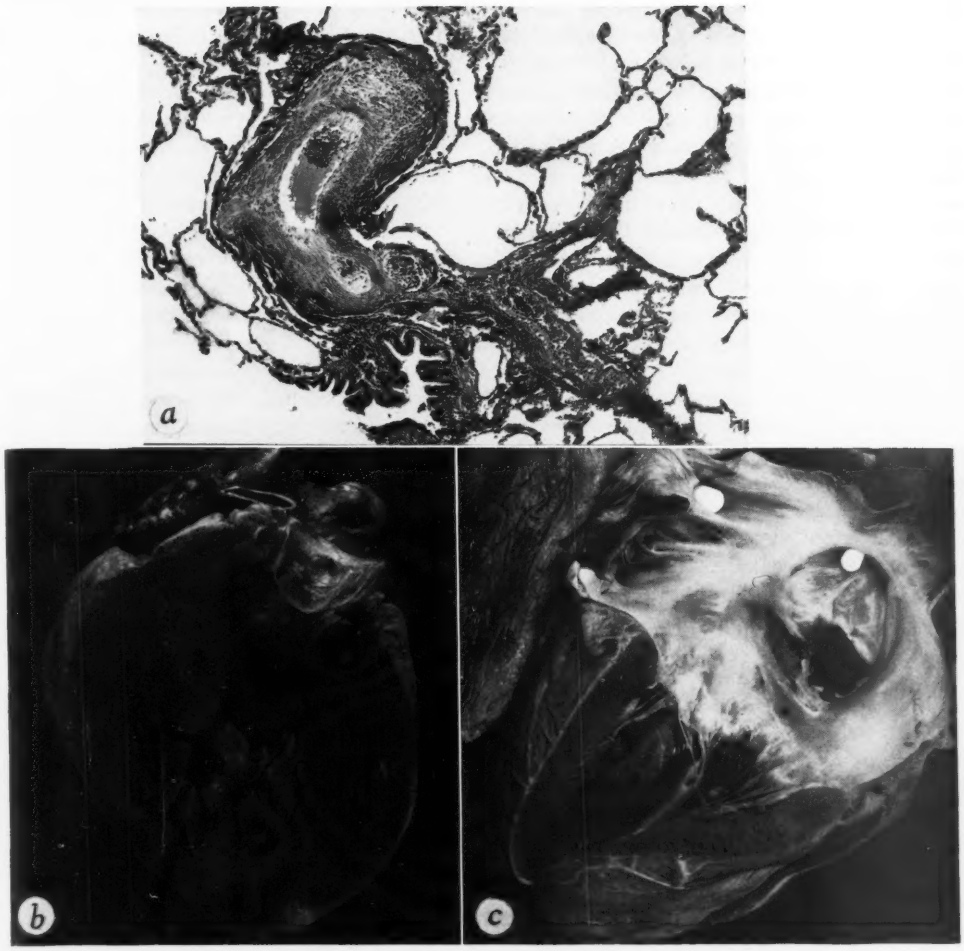

FIG. 12. From a 24-year-old man with atrial septal defect, severe pulmonary hypertension and only a right-to-left shunt. *a*. Photomicrograph of a large muscular artery showing intimal fibrous occlusion (hematoxylin and eosin; reduced from × 135). Such lesions were widely distributed and in addition many foci of arterial necrosis were present in the lung. *b*. The right ventricle. Marked hypertrophy. *c*. The left atrium and ventricle. The atrial septal defect is shown. Probes are present in the right and left upper pulmonary veins. The left ventricle, being of normal thickness, is thinner than the markedly hypertrophied right ventricle illustrated in *b*.

at least, these are so equipped as to suggest that they may have a vasoconstrictive action.

Severe Pulmonary Hypertension. In patients with atrial septal defect who have pulmonary arterial pressures at the levels of systemic arterial pressures, occlusive intimal lesions are present in the large arteries (fig. 12). Vessels involved frequently have diameters in the range of 300 microns. The lesions may be plexiform in nature and identical to those in ventricular septal defect. At this stage the pulmonary vascular bed is difficult to distinguish from that of the high resistance-low reserve type of vascular bed seen in patients with ventricular septal defect.

Necrotizing arterial lesions may occur in the arteries and be associated with thrombosis, which further reduces the capacity of the

vascular bed. Both the intimal fibrous and the necrotizing arterial lesions are considered to be complications of long-standing severe pulmonary hypertension. The necrotizing lesions seem to be commoner in atrial septal defect with severe pulmonary hypertension than in either ventricular septal defect or patent ductus arteriosus. This apparent difference may perhaps be explained by the fact that in atrial septal defect not only may the pulmonary resistance exceed that of the systemic circulation, but the pulmonary pressure may also exceed significantly that in the systemic circulation, since the propelling parts of the circulations are not in communication. In contrast, in ventricular septal defect or patent ductus arteriosus, while the pulmonary vascular resistance may exceed the systemic, the pressures in the 2 circulations cannot be wide apart. The latter phenomenon results from the presence of the communication. As the pulmonary resistance rises above systemic, a right-to-left shunt develops but the 2 pressures will remain at equal levels.

The Effect of the Pulmonary Resistance on Shunts. In contrast to ventricular septal defect, the pulmonary vascular resistance has only an indirect influence on the shunts in atrial septal defect.

To explain this it is first necessary to consider the basis for the shunts in atrial septal defect with normal pulmonary pressure. While in such patients there may be a slightly higher pressure in the left atrium than in the right during parts of the respiratory cycle,[93-95] the 2 atria are, for practical purposes, in free communication through the characteristically large defect.[96] The 2 atria, therefore, operate essentially as a common chamber. The pressure within this functionally common chamber is responsible for filling the 2 ventricles. The right ventricle is thinner than the left. Therefore, the former is more distensible than the latter.[95]

During ventricular diastole when both ventricles are open to the functionally common atrium, a greater volume of blood will flow into the right ventricle than into the left because the former offers a lower resistance to filling. Some of the blood entering the right atrium will be from the anatomic left atrium. This is the blood which constitutes the left-to-right shunt.[97]

Of the blood shunted into the right atrium Swan and associates[98] have shown that there is a greater proportion derived from the right lung than from the left. This is related to the fact that the right pulmonary veins lie closer to the atrial septum and hence to the defect than do the left pulmonary veins. The streams from the right pulmonary veins are thus preferentially shunted through the atrial septal defect.

Even in cases of atrial septal defect with essentially normal pulmonary arterial pressures, there may be a small right-to-left shunt, which is principally derived from the inferior vena cava in contrast to the superior vena cava. This phenomenon is explained by the fact that the inferior caval orifice is directed toward the anterior edge of the atrial septal defect, and the stream of blood is split, some going into the right atrium and some into the left. That which enters the left is, for the most part, directed through the mitral valve into the left ventricle and constitutes the right-to-left shunt. The fact that in this type of atrial septal defect the superior vena cava contributes less to the right-to-left shunt is also explained by anatomic relationships in which the superior caval orifice does not have the close association with the atrial septal defect characteristic of the inferior caval relationships.

Further support for the concept that an anatomic basis underlies the different contribution of the 2 cavae to the right-to-left shunt in the usual variety of atrial septal defect is derived from the fact that when the atrial septal defect lies in an unusual position, such as near the orifice of the superior cava, a preferential right-to-left shunt from the superior vena cava is found.[99]

I have indicated that the basis for the left-to-right shunt in atrial septal defect with normal pulmonary pressures is dependent on the fact that the right ventricle is more distensible than the left. When pulmonary hypertension makes its appearance, the right ventricle hypertrophies in concert with the elevated pulmonary pressure. As the right

ventricle becomes thicker, it becomes less distensible, the difference in distensibility between the left and the right ventricles becomes less and the left-to-right shunt diminishes. At the same time, the degree of right-to-left shunt becomes greater.

In an extreme case of atrial septal defect that we have observed, the pulmonary arterial pressures were higher than the systemic pressures and the right ventricle was thicker than the left (fig. 12*b* and *c*). Functional studies did not reveal the presence of any left-to-right shunt, there being only a right-to-left shunt.

Infants and Children

While atrial septal defect as seen in adults is usually not associated with elevated pulmonary resistance, it is well to consider that at the time of birth and during infancy, quite a different situation might have existed. Many facts yet need to be accumulated regarding the hemodynamics in the newborn with atrial septal defect. Certain hypotheses may be developed, however.

Realizing that in the newborn the 2 ventricles are of the same thickness and therefore probably have the same characteristics with respect to distensibility, a shunt through the atrial septal defect might be of very small magnitude, and with an unknown direction. It might be entirely right to left at this early period, as in fetal life. With the normal tendency for the pulmonary vascular resistance to fall after birth, the pulmonary and right ventricular pressures would also tend to fall, leading to the establishment of a left-to-right shunt. Hence while the pulmonary vascular resistance would fall, pulmonary arterial pressure might remain elevated because of the increased pulmonary flow in the presence of pulmonary vessels that have not yet undergone complete postnatal evolution.

While it is reasonable to suspect that in early postnatal life patients with atrial septal defect have an elevated pulmonary arterial pressure, it is realized that in time, at least in the usual instance of this defect, the pulmonary resistance falls to such a degree that the pulmonary pressure is normal in spite of the increased pulmonary flow. What is not known is whether the change from the early stage, when the pulmonary arterial pressure seems to be elevated and the left-to-right shunt small, to the later stage when the pressure is normal and the shunt large represents a sudden or a gradual change. Moreover, the exact dynamics involved in changing from the high-resistance stage of the newborn to the low-resistance stage of the adult are still not known. A further unanswered question remains concerning the occasional child with atrial septal defect and pulmonary hypertension. Does this represent the same phenomenon of intimal occlusive lesions that characterizes the adult who develops pulmonary hypertension, or does this represent the maintenance of the pulmonary hypertension that is hypothesized as being present in the neonatal period?

Obstruction to Pulmonary Venous Flow

Knowledge concerning the pulmonary vascular response to obstruction to pulmonary venous flow was acquired before that concerning the pulmonary vascular responses in the congenital malformations, which I have already discussed. This knowledge was derived initially from the study of acquired mitral stenosis, but it is applicable not only to congenital mitral stenosis, but also to a variety of other congenital conditions that have as a common factor the obstruction to pulmonary venous outflow. In addition to congenital mitral stenosis, which is rare, these include congenital stenosis of the pulmonary veins (principally cor triatriatum), endocardial sclerosis, and chronic failure of the left ventricle from a variety of causes including mitral insufficiency, coarctation of the aorta, and aortic stenosis.

The first approach to an understanding of the interrelationships between the cardiac disease and the response of the pulmonary vessels was obtained by the demonstration that in acquired mitral stenosis the pulmonary arterioles are thickened.

I had the privilege of being an Assistant at the Mallory Institute of Pathology of the Boston City Hospital in training under Dr. Frederic Parker when he and Weiss[100] prepared their now classic and first definitive ar-

ticle on the subject. Subsequent to this demonstration, many other authors have confirmed the observation that in acquired mitral stenosis the pulmonary arteries and arterioles show medial hypertrophy. Henry[101] stressed that segments of arterioles that are normally without a muscular media develop a muscular media. Heath and Whitaker[102] confirmed this. Intimal proliferation may be a secondary phenomenon, although this change may perhaps simply be an aging phenomenon. A number of authors have indicated that controls at comparable ages show similar intimal lesions. Patients with congenital conditions causing obstruction to pulmonary venous flow show qualitatively similar changes, but in general the changes are more severe than in acquired disease.

In congenital cases, not only is there striking medial hypertrophy of arteries and arterioles, but there is unusual prominence of the elastic membranes of the small arteries and of the arterioles.

The functional significance of the hypertrophic changes in the small pulmonary arteries in mitral stenosis was suspected by Borden and associates[103] and supported by further observations of Dexter and associates.[12]

The basic problem involves obstruction to pulmonary venous flow. Unless compensating mechanisms existed, the elevated pressure in the system proximal to the obstructed mitral valve would be similar. This means that the pulmonary capillary pressure would be the same as pulmonary arterial pressure and at a level well above the threshold for development of pulmonary edema. This hypothetical situation, however, does not usually obtain. The fact is that there is a disproportion between the pressures within the pulmonary arteries as opposed to the pulmonary capillaries, the former being considerably higher than the latter. Explanation of such a phenomenon requires the recognition that an obstructive element exists between the pulmonary arteries and the pulmonary capillaries. Such an obstruction could be brought about either by an anatomic or a functional basis for high resistance to flow through the pulmonary arterioles. This correlates well with the anatomic findings in which not only the thickened arterioles could exert a vasoconstrictive effect, but also the thickened vessels can be looked on as being less distensible than thinner vessels, and consequently, as representing a site of increased resistance to flow. The principles given regarding acquired mitral stenosis apply equally to the cases with a congenital basis for obstruction to pulmonary venous flow regardless of the anatomic site of the basic malformation.

The occurrence of pulmonary edema in patients with this functional type of arrangement may perhaps be due to temporary failure of a vasoconstrictive phenomenon at the pulmonary arteriolar level. Were this to occur, the flow through the pulmonary arterioles would increase. Since the pulmonary venous obstructive factor may be looked on as remaining constant and representing a high resistance to flow, the increased volume in the pulmonary capillaries would be associated with an increase in pressure at this level. Were this to rise sufficiently high, pulmonary edema would result. With this view in mind, it is possible that some cases of this functional category of congenital malformations may develop pulmonary edema, not from heart failure, but rather from pulmonary arteriolar failure.

I trust that in the foregoing I have conveyed the concept that in many varieties of congenital cardiac disease the responses of the pulmonary vessels are of paramount importance in regulating the circulation.

In some instances the pulmonary vascular responses may be considered an integral part of the cardiac malformation. In other instances they may be complications.

With varying pulmonary vascular response the same anatomic defect is associated with varying functional manifestations.

While certain interrelationships are better recognized today than they were a decade ago, there are doubtless many still to be uncovered.

Particularly wanting are explanations of mechanisms for most of the recognized responses. There is much still to be done.

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Medical Eponyms

By Robert W. Buck, M.D.

Graham Steell Murmur. This was described by Graham Steell (born 1851) M.D., Assistant Physician to the Manchester Royal Infirmary, in the *Medical Chronicle* (Manchester) 9: 182–188 (December) 1888, under the title "The Murmur of High-Pressure in the Pulmonary Artery."

"I wish to plead for the admission among the recognised auscultatory signs of disease *of a murmur* due to pulmonary *regurgitation, such regurgitation occurring independently of disease or deformity of the valves, and as the result of long-continued excess of blood pressure in the pulmonary artery.*

"In cases of mitral obstruction there is occasionally heard over the pulmonary area (the sternal extremity of the third left costal cartilage), and below this region, for the distance of an inch or two along the left border of the sternum, and rarely over the lowest part of the bone itself, a soft blowing diastolic murmur immediately following, or, more exactly, running off from the accentuated second sound, while the usual indications of aortic regurgitation afforded by the pulse, etc., are absent. The maximum intensity of the murmur may be regarded as situated at the sternal end of the third and fourth intercostal spaces. When the second sound is reduplicated, the murmur proceeds from its latter part. That such a murmur as I have described does exist, there can, I think, be no doubt."

Clinical and Anatomic Features in Five Hundred Patients with Fatal Acute Myocardial Infarction

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An autopsy series of 500 patients who died with anatomic evidence of acute myocardial infarction is reviewed. The incidence of various clinical and anatomic features is presented. The clinical and anatomic features of patients who died from the first attack of myocardial infarction is compared with those of patients dying after repeated attacks. Similarly, various other features were studied, such as the time that elapsed between the onset of symptoms and death and also the presence or absence of old myocardial infarcts.

ACUTE myocardial infarction is one of the most common causes of death in the United States. Considerable data are available regarding some clinical and anatomic features, but more information must be compiled before the disease is fully understood.

During the period 1910 to 1954 autopsies were performed in the Department of Pathology of Washington University on 8,183 adults (over 20 years of age) from Barnes Hospital. Among these were 500 who died with anatomic evidence of acute myocardial infarction. This autopsy series has been analyzed from the epidemiologic standpoint in several previous reports.[1, 2] In this report we present some of the clinical and anatomic features of these 500 patients with fatal acute myocardial infarction.

The current study has 4 principal purposes: (1) to establish the incidence of various clinical and anatomic features in a large group of patients with fatal acute myocardial infarction; (2) to relate various characteristics to the time that elapses between the onset of symptoms and death; (3) to compare the clinical and anatomic features of patients who die from the first attack of acute myocardial infarction with those in patients who die after repeated attacks; (4) to determine the differences that exist between patients whose condition was correctly diagnosed during life and those in whom the diagnosis of acute myocardial infarction was not made clinically (but who were found to have acute myocardial infarction at autopsy).

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This study was supported in part by grant H-1820 from the National Heart Institute, Institutes of Health, Public Health Service, Bethesda, Md., and in part by the Life Insurance Medical Research Fund.

MATERIAL AND METHODS

The clinical and autopsy records of the 500 patients with acute myocardial infarction were reviewed and pertinent clinical and anatomic features were tabulated for each patient. The resulting tables included more than 20,000 separate entries and these are summarized in this report. Patients were studied as follows:

1. *Elapsed Time Between the Onset and Death.* Among the 500 autopsied patients with acute myocardial infarction were 429 patients who died within 3 weeks after the onset of recognizable clinical symptoms. This portion of our report is limited to these 429 and hence does not include patients in whom the symptoms were so vague as to make clinical dating of the infarct impossible, even in retrospect. Also excluded from the entire study are patients who died so soon after the onset of symptoms that no anatomic changes could be recognized. These 429 patients were classified into 5 subgroups according to the time that elapsed between the onset of symptoms and death, and various clinical and anatomic features were determined for each subgroup and for the entire group.

2. *Presence or Absence of Old Myocardial Infarcts.* Two hundred and thirty-nine of the 500 patients had anatomic evidence of previous myocardial infarction (old infarcts). The clinical and anatomic features of these patients were compared with the characteristics of the remaining 261 patients with no evidence of previous myocardial infarction.

3. *Whether or not the Correct Clinical Diagnosis was Made During Life.* The diagnosis of acute myocardial infarction was not made clinically on 97 of the 500 patients with anatomic evidence of acute

TABLE 1.—*Some Clinical and Anatomic Features of Four Hundred and Twenty-nine Autopsied Patients with Acute Myocardial Infarction Whose Infarcts Could Be Dated by the Clinical History**

	Survival days after onset of symptoms												
	Less than 2 days		2–4 days		5–7 days		8–14 days		15–21 days		Total		
	M	F	M	F	M	F	M	F	M	F	M	F	M & F
No. of pts.	58	20	66	33	53	22	72	48	36	21	285	144	429
Ave. age, yrs.	62	60	62	67	60	64	61	63	58	66	61	64	62
More than 10% overweight† %	40	45	35	51	34	46	29	40	25	48	34	45	38
Hist. of diabetes, %	7	20	11	36	15	36	18	38	8	24	13	32	19
Hist. of hypertension, %	35	65	60	73	47	77	61	67	58	81	53	72	59
Hist. of congestive failure, %	36	55	33	57	38	60	51	52	50	62	41	56	46
Hist. of angina, %	52	40	56	63	49	50	57	27	61	37	55	42	51
Temp. over 39 C. %	2	0	21	15	30	27	21	29	31	48	20	24	21
Gallop rhythm, %	9	25	20	9	19	27	16	23	17	29	16	22	18
Friction rub, %	2	5	8	0	11	5	8	10	6	5	7	6	7
Systolic pressure < 90, %	28	20	18	27	26	27	17	10	17	10	21	18	20
NPN over 80 mg., %	20	0	13	14	23	0	16	15	19	13	18	10	16
Hb. 9 Gm. or less, %	8	27	8	0	8	11	6	7	9	11	7	11	8
WBC > 20,000, %	30	9	24	13	20	28	17	24	25	19	21	18	19
Pulse > 130, %	10	0	15	12	4	9	8	8	3	9	9	8	9
Ward patients, %	22	42	26	33	33	53	28	45	33	32	29	42	33
Private patients, %	78	58	74	67	67	47	72	55	67	68	71	58	67
Chest pain, %	60	65	74	61	70	50	61	50	67	76	66	58	64
Marked dyspnea, %	22	40	40	30	36	18	30	42	47	38	34	35	34
Diagnosis missed, %	21	20	18	9	9	18	25	27	17	24	19	20	19
Location of infarct, ant., %	43	55	41	33	31	27	32	41	52	19	40	36	38
Location of infarct, post., %	28	15	32	37	29	27	38	27	23	43	32	30	31
Location of infarct, sept., %	3	15	6	15	6	9	10	17	11	14	7	14	10
Location of infarct, other, %	26	15	21	15	34	37	20	15	14	24	21	20	21
Size of infarct, large, %	12	25	32	18	34	27	29	27	31	14	27	23	26
Size of infarct, medium, %	60	60	57	70	47	59	58	44	47	57	55	56	55
Size of infarct, small, %	28	15	11	12	19	14	13	29	22	29	18	21	19
Healed infarct, %	50	35	52	52	42	41	49	44	47	48	48	44	47
Thromboembolism, %	24	35	15	36	32	36	53	46	56	66	35	45	38
Mural thrombi, %	20	30	44	52	47	45	57	50	47	48	43	47	44
Rupture, %	3	10	11	6	8	0	4	4	6	0	6	4	5
Bronchopneumonia, %	9	10	26	24	28	32	24	19	14	62	21	27	23
Effusion in pleural or abd. cavity, %	10	25	35	45	34	41	31	37	22	48	27	40	31
Ave. wgts. of heart, Gm.	515	435	540	465	545	490	565	450	560	470	545	465	520
Ave. wgts. of kidneys, Gm.	325	285	365	270	365	305	360	310	350	300	355	295	335
Ave. wgts. of lungs, Gm.	1315	950	1360	1090	1325	1060	1285	975	1370	925	1320	990	1210

* The percentage listed (except in 3 instances) is that of autopsied patients of the sex and group indicated with the characteristic designated. The exceptions are "NPN", "Hb" and "WBC." In these instances the percentage indicated is based only on patients on whom the designated procedure was performed.

† According to the tables for ideal weights of the Metropolitan Life Insurance Co.

myocardial infarction. The characteristics of these 97 patients were compared with those of the 403 patients who were diagnosed correctly during life.

RESULTS

The results are summarized in tables 1 and 2.

1. *Analysis of those whose Infarcts Could be Dated Clinically.* The 429 patients were classified into 5 subgroups according to the time that elapsed between the onset of symptoms and death and various clinical and anatomic characteristics were determined for each subgroup (table 1) and for the entire group of 429. Most characteristics appear to be similar in the 5 groups. The incidence of a few characteristics appeared to change with the elapse of time between the onset of symptoms and death. Certain of these characteristics were subjected to statistical analysis by comparing the "less-than-2-days group" in table 1 with the "more-than-2-weeks group." The characteristics thus compared and the p values obtained for the differences are as follows: Temperature over 39 C. ($p < 0.01$), systolic pressure less than 90 mm. Hg ($p = 0.05$), history of "hypertension" ($p = 0.01$), mural thrombi in the heart ($p = 0.02$), thromboembolic phenomena

TABLE 2.—*Comparison Between Ninety-Seven Patients with Anatomic Evidence of Acute Myocardial Infarct Misdiagnosed Clinically and Four Hundred and Three Patients with Anatomic Evidence of Acute Myocardial Infarct Correctly Diagnosed Clinically*

	Diagnosis missed clinically			Diagnosis made clinically		
	M	F	M & F	M	F	M & F
No. of patients	66	31	97	269	134	403
Ave. age, Years	62	64	63	61	64	62
Chest pain, %	18	13	16	77	68	73
Dyspnea, %	38	40	39	33	36	34
Small infarct, %	50	45	48	14	16	15

elsewhere than in the heart ($p < 0.01$), pleural or peritoneal effusions ($p = 0.02$), heart weight ($p = 0.5$), and bronchopneumonia ($p < 0.01$). It is apparent that all of the differences thus compared are statistically significant except that between the heart weights.

2. *Analysis of those with Evidence of Old Infarction in Addition to Acute Infarction.* Forty-eight per cent of the 500 patients had anatomic evidence of previous myocardial infarction (49 per cent of the men and 45 per cent of the women). No significant difference was present between the average ages of the patients in the 2 groups (with and without old myocardial infarcts). The body weights and weights of hearts were similar in the 2 groups. No consistent differences were noted in size and location of the recent infarcts in the 2 groups.

Only 25 per cent of the patients with anatomic evidence of old infarcts gave a clinical history of previous infarction. The interval that elapsed between the earliest previous infarct and death was stated in the records of 37 patients, and the average of these intervals was 3.3 years (range 6 months to 13 years).

3. *Analysis of those with Anatomic Evidence of Acute Infarction who did not have a Clinical Diagnosis of Acute Infarction.* Examination of the clinical records disclosed that the diagnosis of acute myocardial infarction was made clinically in 403 (81 per cent) of the 500 patients, and was not made in the remaining 97 (19 per cent). Sixty-six were men (19.5 per cent of the entire 335 men) and 31 were women (18.5 per cent of the 165 women). The average age of the 66 men was 62 and of the 31 women, 64; these average ages are similar to those for the entire group of 500.

Small infarcts were more than 3 times as common among these 97 patients than among the remaining 403 patients ($p < 0.01$). However, there was no significant difference in the location of the infarcts among the 97 patients as compared with the remaining 403. Only 18 per cent of the 66 men and 13 per cent of the 31 women complained of chest pain during the course of their illness. The corresponding figures for chest pain among the 403 patients on whom the correct diagnosis was made clinically were 77 per cent for men and 68 per cent for women ($p < 0.01$ for the difference for each sex). Examination of the clinical records of the 97 patients for complicating circumstances associated with the terminal illness disclosed that 29 per cent had had a major operation within 1 month prior to death, 13 per cent had clinical evidence of cerebral infarction or hemorrhage, and 3 per cent were psychotic. Most of the remaining 55 per cent of the 97 patients were diagnosed as having "arteriosclerotic heart disease" or "hypertensive cardiovascular disease" without acute myocardial infarction. Electrocardiograms were taken on 75 per cent of the 97 patients and some evidence of coronary insufficiency was observed in most. However, none showed changes that were considered diagnostic of acute myocardial infarction.

DISCUSSION

Group 1

Angina Pectoris. It is rather surprising that only one half of these 429 patients had a history of previous angina pectoris. The first explanation that occurred to us was that many of the patients who died in the first few days were unable to give an adequate history. However, this explanation proved untenable because those who died later (1 to 3 weeks after onset of symptoms) did not have a higher incidence of angina pectoris than those who died in the first few days. Thus, it appears that fatal acute myocardial infarction often strikes down the unsuspecting victim without previous warning. The corresponding figures

for the incidence of prior angina pectoris in other series (clinical and autopsy) vary from 20 per cent to 70 per cent.[3-6]

Dyspnea. Dyspnea is considered to be one of the most common symptoms of acute myocardial infarction.[7, 8] Although some degree of dyspnea was undoubtedly present in most of our patients, it was considered severe enough to warrant discussion in the clinical records in only 34 per cent. Dyspnea was not more common in those who died soon after the onset of symptoms than in those who died later.

Shock, Markedly Elevated Temperature, Leukocyte Count of Over 20,000/mm.^{3}, Gallop Rhythm, and Marked Tachycardia. These characteristics are all known to indicate a poor prognosis.[9-12] However, no single 1 was common in this series.

Chest Pain as Part of the Chief Complaint. According to the medical histories only 64 per cent of these 429 patients with fatal acute myocardial infarction complained of chest pain (including "soreness," "oppression," and "discomfort,") and the incidence of chest pain was not related to the interval between the onset of symptoms and death. Corresponding figures from other series vary widely.[13-15] The highest incidence of chest pain was that reported by White[16] who found 96 per cent of 56 patients with acute myocardial infarction (proved at autopsy) had chest pain.

Economic Status. The economic status of our patients (as indicated by their ability to pay for medical care) did not appear related to the incidence of acute myocardial infarction, nor to the number of days that elapsed between the onset of symptoms and death. The ratio of ward to private patients in this series was similar to the ratio of ward to private patients in the entire Barnes Hospital autopsy population.

Group 2

All of the clinical and anatomic characteristics of these 239 patients were similar to the characteristics of patients who died of their first episode of acute myocardial infarction. It is interesting that only 25 per cent of these 239 patients with anatomic evidence of old myocardial infarction gave a history of previous myocardial infarction.

Group 3

Acute myocardial infarction in its classic form can be diagnosed by any medical student. However, the fact that 19 per cent of our patients with anatomic evidence of acute myocardial infarction were not diagnosed clinically emphasizes that acute myocardial infarction does not always manifest itself in "classic form."

Only 16 per cent of these 97 patients complained of chest pain, and only 39 per cent had marked dyspnea during the course of their illness. In almost half of these 97 patients the clinical picture was obscured by complicating circumstances (major operations, cerebral infarction or hemorrhage, or psychoses).

The only anatomic characteristic that we found to be different in this group (as compared with those who were diagnosed correctly during life) was the size of the myocardial infarct. Approximately one-half of the 97 patients who were not diagnosed correctly during life as having acute myocardial infarction had "small" infarcts. Only 12 per cent of the remaining 403 patients had "small" infarcts.

Summary

Some clinical and anatomic features have been presented from 500 autopsied patients who died with acute myocardial infarcts. These patients have been classified in several ways:

1. According to the time that elapsed between the onset of symptoms and death. The time of onset of acute myocardial infarction could be dated clinically (at least in retrospect) for 429 of the 500 patients. Only half of these patients gave a history of previous angina pectoris. Thus it appears that fatal acute myocardial infarction often occurs without previous warning. The 429 patients were divided into 5 subgroups according to the time that elapsed between the onset of symptoms and death. Comparisons are made of the features in the 5 subgroups.

2. According to the presence or absence of old myocardial infarcts. Almost half of the patients had anatomic evidence of old infarction in addition to their recent myocardial infarct. The clinical and anatomic features that were studied in the patients with associated old myocardial infarcts were all similar to those in the patients without associated old infarcts. It is interesting to note that only 25 per cent of the patients with old myocardial infarcts gave a history of previous myocardial infarction.

3. According to whether or not the correct clinical diagnosis was made during life. In 19 per cent of the 500 patients with anatomic evidence of acute myocardial infarction the correct diagnosis was not made during life. In many of these patients complicating features (such as major surgical operations) were present that obscured the clinical picture. Chest pain was much less common and small infarcts were much more common in these patients than in those who were diagnosed correctly during life.

Summario in Interlingua

Es presentate certe characteristicas clinic e anatomic de 500 patientes necropsiate, morte con acute infarcimento myocardiac. Iste patientes esseva classificate in plure manieras:

1. Secundo le intervallo de tempore inter le declaration del symptomas e le morte. Le tempore del declaration de acute infarcimento myocardial poteva esser fixate (al minus in retrospecto) pro 429 del 500 patientes. Solmente un medietate de iste patientes presentava un historia de previe angina de pectore. Assi il pare que mortal infarcimento myocardial acute occurre frequentemente sin signal premonitori. Le 429 patientes esseva dividite in 5 subgruppos secundo le intervallo inter le declaration del symptomas e le morte. Le characteristicas trovate in le 5 subgruppos es comparate.

2. Secundo le presentia o absentia de ancian infarcimento myocardial. Quasi un medietate del patientes habeva vestigios anatomic de ancian infarcimento, a parte lor recente infarcto myocardial. Le characteristicas clinic e anatomic studiate in le patientes con associate vestigios de ancian infarctos myocardial esseva omnes simile al constatationes trovate in patientes sin ancian infarctos. Il es interessante notar que solmente 25% del patientes con ancian infarctos myocardial habeva reportate le previe occurrentia de infarcimento myocardial.

3. Secundo que si o non le correcte diagnose clinic esseva establite durante le vita del patiente. In 19 pro cento del 500 patientes con probas anatomic de acute infarcimento myocardial, le correcte diagnose non esseva establite durante le vita del patiente. In multes de iste casos, complications (p. ex. major operationes chirurgic) esseva presente, le quales obscurava le aspectos clinic. Dolores thoracic esseva multo minus frequente e parve infarctos esseva multo plus frequente in iste gruppo de patientes que in illes pro qui le correcte diagnose habeva essite establite durante le vita.

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Keys, J. R., Dry, T. J., Walters, W., and Gage, R. P. Cholecystectomy in Patients with Coronary Heart Disease. Proc. Staff Meet., Mayo Clin. **30:** 587 (Dec.), 1955.

A study was undertaken to determine (1) the operative risk of cholecystectomy for patients with coronary heart disease and (2) whether removal of a diseased gallbladder influenced the subsequent course of the patient with coronary heart disease. There were 100 patients in the series. The actual surgical procedure was well tolerated with no deaths or other serious complications on the operating table. Three patients died in the hospital; one from acute pancreatitis, another from pancreatic necrosis, and the third patient died on the seventeenth postoperative day. This patient had cardiac failure and suffered from a cerebrovascular accident earlier in the postoperative course, neither of which seemed directly responsible for his death. The postoperative morbidity rate was not unusual for intra-abdominal procedures in patients of the age of these patients.

The survival rate of this group of patients 6 years after operation was 71 per cent as compared with 84 per cent in the normal population of similar sex and age constitution. This study establishes the relatively low risk of cholecystectomy in patients with symptomatic coronary heart disease and emphasizes the dangers inherent in the complications of chronic biliary disease itself. Such complications must be considered even more serious in patients with coronary heart disease. It is doubtful whether removal of a diseased gallbladder influences the course of coronary artery disease directly but it is likely that life may be prolonged by preventing the serious complications of biliary disease by performance of cholecystectomy preferably during the quiescent phases of gallbladder disease.

SIMON

Relation of the Postcommissurotomy Syndrome to the Rheumatic State

By DANIEL L. LARSON, M.D.

The postcommissurotomy syndrome is a frequent troublesome complication after mitral valve surgery, the etiology of which is still obscure. In this study of 137 patients who survived surgery the clinical features of this complication are carefully detailed, possible associated conditions are studied, and pathologic findings in the atrial appendages are analyzed. In particular, the relation of this syndrome to the rheumatic state is critically examined.

SINCE the introduction of a practical method for the surgical treatment of mitral stenosis,[1, 2] a large number of patients have undergone this procedure. Soloff and his colleagues[3] described the onset of chest pain and fever in the second or third week after operation of 47 out of 179 individuals. Since that time several reports have appeared from other clinics[4-12] describing similar complications following this operation. In most series, between 10 and 40 per cent of the patients develop this distressing disease known as the "postcommissurotomy syndrome."

Characteristically, the patient has a normal postoperative course until the second or third week. Then chest pain begins, which often radiates into the shoulders or neck. The pain does not necessarily involve the incisional area and may be pleuritic in nature. It is accompanied by an elevation in temperature, erythrocyte sedimentation rate, and white blood cell count. A pleural or pericardial friction rub may reappear, and x-ray evidence of inflammation of the pleura is often demonstrable. There is no serologic or bacteriologic evidence of a recent infection with group A hemolytic streptococcus. There is no electrocardiographic evidence of rheumatic carditis, and the peripheral joints are not involved. The duration of the fever is variable, and the patients may have several such attacks over a long period of time. The presence or absence of the phenomenon apparently bears no relation to the ultimate functional result of the operation. It is the purpose of this report to present evidence to suggest that most attacks of this condition are probably not rheumatic activity.

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CLINICAL MATERIAL

This report includes observations on 154 patients undergoing exploration of the left atrium, with or without mitral valve commissurotomy, at the Columbia-Presbyterian Medical Center in New York, during the period 1950 through 1955.

Seventeen patients died within the period of a few days after operation. Many of the deaths occurred in group IV patients, and before much operative experience had been accumulated. Since these patients did not live long enough to develop the postcommissurotomy syndrome, they are not included in the report. Nine died as a result of embolization, and all of these patients had a thrombus in the atrial appendage, calcification of the valve margins, or both; only 1 had normal sinus rhythm. Five patients died in severe congestive heart failure, and 3 died of ventricular fibrillation.

Of the 137 survivors, 51 individuals (37 per cent) had 78 attacks of delayed onset of unexplained chest pain, fever (rectal temperature 100.2 F. or more for 2 days in succession) and other evidence of inflammation. This rate of attack is undoubtedly falsely low because some of the patients had been followed for a relatively short time after operation. Furthermore, the 78 attacks were severe enough to require hospitalization, while other attacks occurred in patients who were treated at home and ran a milder clinical course. The postcommissurotomy syndrome usually appeared within 3 weeks after operation. In no case was there circumstantial evidence of rheumatic activity such as recovery of group A hemolytic streptococci from the throat, elevation in circulating antibody titers to one of the streptococcal antigens, or lengthening of the P-R interval on the electrocardiogram to values in excess of 0.20 sec. In this report the clinical findings of the patients who did and the patients who did not sustain attacks of this syndrome are compared.

Results

Historical Data. Only half of the individuals in each group had a definite history of an acute attack of rheumatic fever, and about 5 per cent in each group had scarlet fever in childhood. Twenty per cent of those without the postcommissurotomy syndrome had chorea while only 4 per cent of those with it gave such, a history. The age at which heart murmurs were first documented is approximately the same in both groups—usually before the age of 30.

Of the 137 surviving patients, 79 per cent are women, an expected finding, since rheumatic mitral valvular disease is more common in women. It is of considerable interest that the postcommissurotomy syndrome was seen in women more than twice as often (44 per cent) as in men (16 per cent).

The symptoms of congestive heart failure first appeared in the second and third decade in both groups—often occurring in the last trimester of pregnancy. In those developing congestive heart failure during pregnancy, the symptoms often disappeared following delivery, only to reappear several years later in the form of progressive decrease in cardiac reserve. Three patients were operated upon while in the first trimester of pregnancy with an uneventful postoperative course. One of these patients has since had a normal full-term spontaneous delivery. Two other patients had developed congestive heart failure with previous pregnancies but, after mitral commissurotomy, were able to go through normal pregnancies without symptoms of cardiac failure. None of these individuals developed the postcommissurotomy syndrome.

Rheumatic Activity Before Operation. The possibility of rheumatic activity must be ruled out before operation in order to avoid a stormy postoperative course. Individuals suspected of having activity may have low-grade pains in the extremities, fever, elevation in the erythrocyte sedimentation rate, conduction changes in the electrocardiogram, and other evidence of acute rheumatic fever. The usual management of patients with these inflammatory changes was bed rest over a relatively long period of time until the values returned to normal or until there was no further improvement. Of the 137 patients, 21 (15 per cent) fell into this group. Eleven of them escaped the postcommissurotomy syndrome and 10 had 1 or more attacks (table 1). Since the over-all incidence of the postcommissurotomy syndrome in this series is at least 37 per cent, and its incidence in individuals suspected of rheumatic activity before operation was approximately 50 per cent, there is at most only a small increase in the risk of subsequent occurrence of the postcommissurotomy syndrome among those showing inflammatory changes prior to operation ($p = < 0.01$).

Seasonal Incidence. Attacks of rheumatic fever usually have their highest incidence during the spring and fall of the year. If the postcommissurotomy syndrome is associated with rheumatic activity, it is possible that such a seasonal incidence would be recognized. In this series, there was a slight increase in the incidence of the postcommissurotomy syndrome during the spring of the year, but this was also the period when the largest number of operations were performed. It would appear, therefore, that there is no seasonal variation demonstrable in the occurrence of the postcommissurotomy syndrome.

Rate of Ambulation. The time of mobilization of patients in the postoperative period conceivably might be related to the incidence of the postcommissurotomy syndrome. This factor is difficult to evaluate, since many of the patients were discharged from the hospital and were not under direct observation before the onset of the syndrome. Progressive mobilization was started on almost all patients before the tenth postoperative day, and the rate at which this proceeded was, in general, related to the degree of improvement in exercise tolerance. There was no difference in the rate of functional improvement among those who developed the syndrome and those who did not. Thus, the rate of mobilization was not implicated as a precipitating factor.

Effect of Prophylaxis. The majority of attacks of the postcommissurotomy syndrome began within 3 weeks after operation. All patients were maintained on large intramuscular doses of penicillin for a week to 10 days after opera-

TABLE 1.—*Incidence of Possible Low-Grade Rheumatic Activity Immediately Before Operation*

	Postcommissurotomy syndrome			
	Absent		Present	
	Number	Per cent	Number	Per cent
"Rheumatic activity"	11	13	10	20
P-R > 0.20 sec.	6	7	6	12
Erythrocyte sedimentation rate, preoperative:				
20–40 mm.	9	10	11	22
>40 mm.	6	7	5	9

tion. Of the 51 individuals with the postcommissurotomy syndrome, 18 patients (35 per cent) developed at least 1 episode while on large dosages of penicillin. Similarly, sulfadiazine in dosage of 1 Gm./day has been shown to prevent recurrences of acute rheumatic fever in the majority of individuals. In this series, 11 patients (22 per cent of those developing the syndrome) sustained their initial attack while on prophylactic sulfadiazine.

Effect of Salicylates and Prednisone. Salicylates in adequate dosage usually suppress evidence of the inflammatory component associated with rheumatic activity. In the group of patients with the postcommissurotomy syndrome, 27 first attacks and 14 recurrences were noted during salicylate therapy. It should be pointed out, however, that the dosages of salicylate were often lower than what may be considered optimal for the suppression of rheumatic activity. Only 8 attacks occurred in individuals receiving 3.6 Gm. or more of salicylate per day.

In this series, adrenal steroids were used as antiinflammatory agents only when the syndrome did not respond satisfactorily to salicylate therapy. There is suggestive evidence that the prophylactic use of adrenal steroids may prevent some attacks of this syndrome.[9] In the present series, there were 3 recurrences in individuals who were being carried on 15 mg. of prednisone daily. These 3 patients had exhibited dramatic improvement when treated with prednisone during their previous attack.

Clinical Course of the Postcommissurotomy Syndrome. The clinical course of the patients who developed the postcommissurotomy syndrome was quite variable. All of the patients were given salicylates if they were not already receiving the drug prophylactically. Half of the patients had a normal temperature and a disappearance of the chest pain within 10 days of the onset of the postcommissurotomy syndrome. The remainder of the group continued to be intermittently febrile with chest pain and an elevated erythrocyte sedimentation rate for as long as 5 weeks. A prolonged course occurred in some patients in spite of therapy considered optimal for the treatment of rheumatic fever. Most of the recurrences of the postcommissurotomy syndrome took place within 2 months of the initial attack, but several patients had repeated episodes for as long as 18 months after the operation.

Subacute Bacterial Endocarditis. Four patients in the present series had a history of subacute bacterial endocarditis treated with antibiotics, from 3 months to 4 years before the operation. Three of these developed at least 1 attack of the postcommissurotomy syndrome in the absence of any clinical or laboratory evidence of subacute bacterial endocarditis. One patient whose postoperative course was complicated by what was thought to be the postcommissurotomy syndrome, developed splenomegaly, anemia, and a positive blood culture for *Streptococcus viridans.* After a course of antibiotics the abnormal findings disappeared. No other patient was shown to have a positive blood culture in the postoperative period.

Thromboembolic Disease. Another consideration in the differential diagnosis of an unexplained postoperative fever is the occurrence of thromboembolic phenomena. One of the factors that predisposes to embolization is an abnormal cardiac rhythm. In the group without the postcommissurotomy syndrome normal sinus rhythm and chronic atrial fibrillation were equal in frequency (table 2). Among those with the syndrome, however, the incidence of normal sinus rhythm was over twice that of chronic atrial fibrillation. There was a correspondingly higher incidence of transient atrial fibrillation in the postoperative period of patients with the postcommissurotomy syndrome than in those without it. It should

TABLE 2.—*Cardiac Rhythm*

	Postcommissurotomy syndrome			
	Absent		Present	
	Number	Per cent	Number	Per cent
Normal sinus rhythm	42	49	36	71
Chronic atrial fibrillation	44	51	15	29
Paroxysmal atrial fibrillation, postoperative	11	13	17	33

TABLE 3.—*Pathologic Findings in Atrial Appendages*

	Postcommissurotomy syndrome			
	Absent		Present	
	Number	Per cent	Number	Per cent
Normal	7	8	1	2
Aschoff bodies	12	14	9	18
Thrombus	26	30	9	18
Calcification of valves	13	15	15	29
Myocarditis	12	14	4	8
Endocarditis	44	51	31	61
Myocardial hypertrophy	53	62	32	63

be noted that thromboembolism was not demonstrated in any of the postoperative episodes of paroxysmal atrial fibrillation, although the incidence of the postcommissurotomy syndrome was much increased.

Calcification of the margins of the valve and thrombus in the atrial appendage increase the risk of embolization following operation.[20-23] Among the 30 patients with recognized thromboembolic episodes, 9 patients died of this complication before they could go on to develop the postcommissurotomy syndrome. All of them had calcification of the valve margins, thromboses in the appendage, or both.

An episode of the postcommissurotomy syndrome appeared in about one-half the remaining 21 patients who developed embolic phenomena. As can be seen in table 3, calcification of the valve margins was more frequent in those who developed the postcommissurotomy syndrome than in those who escaped the disease. In all probability, some of the patients diagnosed as having the postcommissurotomy syndrome were in reality undergoing unrecognized thromboembolic disease. The higher frequency of auricular thrombi among those who escaped the postcommissurotomy syndrome probably reflects the increased incidence of chronic atrial fibrillation in this group.

Pathologic Findings. In table 3 it can be seen that 94 per cent of the atrial appendages showed at least 1 abnormal finding. Aschoff nodules, usually interpreted as evidence of rheumatic carditis, were observed in 15 per cent of the specimens, which is less than reported in some series,[3, 4, 9, 24, 25] but more than in another series.[10] The incidence of Aschoff nodules is more or less directly related to the thoroughness with which a search is carried out. Aschoff nodules were not significantly more common in the group that developed the postcommissurotomy syndrome than in the group that did not.

Anemia. With few exceptions, the preoperative hemoglobin values of all patients were above 12 Gm. per cent. As can be seen in table 4, only 7 per cent of the patients with an uncomplicated postoperative course had significant depressions in hemoglobin levels following operation. In contrast, 46 per cent of patients with the postcommissurotomy syndrome showed a drop in hemoglobin of from 2 to 6 Gm. per cent while undergoing the acute phase. The anemia was hypochromic in character and in many cases the values returned to normal upon oral administration of ferrous sulfate. Reticulocytes, which were counted in only 3 of these patients, ranged from 5 to 10 per cent. The anemia was somewhat surprising, since it could not be explained on the basis of overt blood loss.

Postcommissurotomy Syndrome in the Nonrheumatic Subject. The syndrome of delayed onset of chest pain, unexplained fever, and elevated erythrocyte sedimentation rate has been observed in patients undergoing chest surgery for disease unrelated to rheumatic fever. This syndrome has been seen at the Columbia-Presbyterian Medical Center following valvulotomy for congenital pulmonic stenosis, repair of a coarctation of the aorta, ligation of a patent ductus arteriosus, repair of an interatrial septal defect, lobectomy, and mediastinal exploration for suspected substernal thyroid. None of these patients had any indication of rheumatic fever, past or present.

TABLE 4.—*Postoperative Depression of Hemoglobin (Gm. %)*

Gm. % depression	Postcommissurotomy syndrome			
	Absent		Present	
	Number	Per cent	Number	Per cent
2.1–3	2	2	8	16
3.1–4	2	2	7	14
4.1–5	2	2	6	12
>5	1	1	2	4

Postoperative Rheumatic Activity. Occasionally, patients may have a classical reactivation of rheumatic activity in the postcommissurotomy period. In 1 reported series,[6] 2 patients developed rheumatic fever following commissurotomy, 1 of whom developed definite aortic valvular damage. In our series, 3 patients had exacerbations of rheumatic activity with peripheral joint pains, fever, high erythrocyte sedimentation rate, and prolongation of the P-R interval.

DISCUSSION

Since all the patients operated upon for mitral stenosis have had rheumatic activity in the past, it was reasonable to suspect that the postcommissurotomy syndrome represents an exacerbation of rheumatic fever. In the light of additional clinical experience, however, this position is becoming increasingly difficult to defend. At the present time there is serious doubt that rheumatic activity is responsible for the clinical manifestations of the syndrome in the majority of instances.

Half of the patients coming to commissurotomy give no history of an acute attack of rheumatic fever, and there is no relation between the natural history of the disease process in the preoperative period and the development of the postcommissurotomy syndrome. The risk of this complication in patients with nonspecific low-grade inflammatory reaction in the preoperative period is only slightly increased. Nonspecific inflammatory changes were seen in almost all amputated auricles, but the incidence of the postcommissurotomy syndrome was not significantly increased in those whose auricles showed Aschoff nodules.

Association of trauma with the onset of acute rheumatic fever has been observed many times. In a recent review[13] it was apparent that many patients had a definite antecedent pharyngitis, and, in some cases, the injured area was simply the first one to be involved or was the area involved most severely. Other nonspecific stimuli associated with an exacerbation of rheumatic activity have usually been noted in patients with chronic low-grade activity, and they developed the other indications of the full blown disease such as joint pains and carditis. Trauma or nonspecific stimulation does not explain the variable delay in onset of the syndrome after operation, as well as the multiple recurrences in the absence of such stimuli.

Patients with the postcommissurotomy syndrome do not exhibit any epidemiologic, bacteriologic, or serologic evidence of a group A hemolytic streptococcus infection; furthermore, the complication occurs despite adequate prophylaxis with penicillin or sulfadiazine. An exacerbation of acute rheumatic fever under these circumstances would appear to be most unlikely. Some patients developed the syndrome while on full suppressive dosages of salicylates or prednisone and evidence of inflammatory response could be detected in some individuals for several weeks after institution of a regimen considered optimal for the treatment of rheumatic activity.

If rheumatic fever were the basis for the postcommissurotomy syndrome, some additional residual cardiac damage would be likely after 1 or more severe episodes. Despite several attacks, however, the patients with this complication had just as good a functional result as those who escaped it.

The possibility of subacute bacterial endocarditis must be ruled out in any patient with unexplained fever in the postcommissurotomy period. Several instances of this complication have been reported.[14-19] One patient in our series developed a classical clinical picture of endocarditis. It must be remembered that patients receive antibiotics in large dosage in the postoperative period, which may alter the usual clinical picture of subacute bacterial endocarditis.

A group of signs and symptoms, indis-

tinguishable from the postcommissurotomy syndrome, has been observed in patients undergoing chest surgery in whom rheumatic activity would appear to be excluded. The procedures were done for a variety of congenital cardiovascular lesions and for exploration of the mediastinum. It is apparent then that simple operative disturbance of the contents of the mediastinum may occasionally be associated with an inflammatory response of the delayed type.

It is established that an occasional patient may have an easily recognizable exacerbation of rheumatic fever in the postoperative period. Even though there may be striking improvement of exercise tolerance after operation, there is therefore no justification for elimination of measures to prevent recurrences of rheumatic fever or subacute bacterial endocarditis.

Among other causes of postoperative fever that may be considered are drug sensitivity, idiopathic pericarditis, and thromboembolic disease. In our series, the patient most likely to develop the postcommissurotomy syndrome is a woman with a normal sinus rhythm before operation, calcification of the margins of the valves, and an auricular thrombus, who has an episode of atrial fibrillation.

Summary

Of 137 patients surviving mitral commissurotomy, 51 patients sustained 78 attacks of the postcommissurotomy syndrome. None of the patients had evidence of a recent group A hemolytic streptococcus infection, and the attacks were not prevented by the administration of sulfadiazine, penicillin, salicylates, or prednisone. In this series, female patients with normal sinus rhythm before operation and with a bout of atrial fibrillation in the postoperative period were the most likely to develop this complication. An unexplained hypochromic anemia occurred in almost half of the patients during an episode of the postcommissurotomy syndrome. Subacute bacterial endocarditis occurred in 1 patient, and easily recognized acute rheumatic fever developed in 3 patients during the postoperative period. A disorder indistinguishable from this syndrome may occur in patients following chest surgery for a variety of congenital or acquired diseases that are unrelated to rheumatic fever. Although typical rheumatic fever may occasionally recur in the postoperative period, it is concluded that the majority of individuals with the postcommissurotomy syndrome are probably not undergoing an exacerbation of rheumatic activity.

Summario in Interlingua

Inter 137 patientes supervivente a commissurotomia mitral, 51 suffreva attaccos del syndrome post-commissurotomic. Nulle de iste 51 patientes exhibiva signos de un recente infection per streptococcos hemolytic gruppo A, e le attaccos non esseva prevenite per le administration de sulfadiazina, penicillina, salicylatos, o prednisona. In le serie hic reportate, patientes feminin con normal rhythmos sinusal ante le operation o con un episodio de fibrillation atrial durante le periodo postoperatori se monstrava le plus susceptibile a disveloppar le syndrome post-commissurotomic. Un inexplicate anemia hypochromic occurreva in quasi un medietate del patientes durante episodios de iste complication. Subacute endocarditis bacterial occurreva in 1 patiente, e febre rheumatic in formas facilemente recognoscible se disveloppava in 3 patientes—ambes durante le periodo post-operatori. Un disordine non distinguibile ab le syndrome post-commissurotomic pote occurrer in patientes subjicite a operationes thoracic pro varie congenite o acquirite morbos non connectite con febre rheumatic. Ben que typic febre rheumatic pote recurrer in certe casos durante le periodo post-operatori, nostre datos supporta le conclusion que le majoritate de individuos con le syndrome post-commissurotomic non suffre un exacerbation del activitate rheumatic.

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Legal Judgments and Clinical Diagnosis

General propositions do not decide concrete cases. The decision will depend on a judgment or intuition more subtle than any articulate major premise.—O. W. Holmes, Jr., 1905.

Ebstein's Anomaly

By S. Gilbert Blount, Jr., M.D., Malcolm C. McCord, M.D.,† and Ira J. Gelb, M.D.

Four cases of Ebstein's anomaly are described, revealing that the clinical features permit diagnosis in the majority of instances and that cardiac catheterization affords precise confirmation of the diagnosis. The occurrence of this anomaly in acyanotic adults is pointed out, and the similarity to acquired valvular rheumatic heart disease is stressed.

THE congenital cardiac defect known as Ebstein's anomaly has been recognized as a pathologic entity for 90 years.[1] The first 80 years of this period constituted a relatively dormant era characterized by sporadic descriptions of the lesion at postmortem examination and by intimation that clinical recognition of this anomaly was not possible.[2] Knowledge regarding Ebstein's anomaly has accumulated rapidly following the introduction of cardiac catheterization. A rapidly expanding body of information has accumulated in the literature in the past 10 years that has totally dispelled the myth of the diagnostic impregnability of Ebstein's anomaly.[3-13] This recent experience has permitted the establishment of a definitive pattern of diagnostic clinical features. These features, when applied in the younger age patients, should lead promptly to the recognition of this anomaly.

The less well described occurrence of Ebstein's anomaly is in adults without cyanosis. This type of patient with Ebstein's anomaly constitutes a more formidable diagnostic challenge than does the cyanotic child in view of the possible confusion with acquired cardiac lesions. A description of the congenital malformation first described by Ebstein in 1866 is considered to be pertinent at this time. Although the details in the individual case have varied somewhat, in general this malformation consists of an abnormality of the leaflets and origin of leaflets of the tricuspid valve. This consists of a fusion of the leaflets, particularly the septal and posterior leaflets, into a membranous structure extending into the cavity of the right ventricle and separating the right ventricle into a proximal and distal chamber. The proximal portion, which consists of the sinus of the right ventricle, is continuous with the right atrium, while the distal portion, composed of the outflow tract of the right ventricle, functions as the right ventricle. The anterior leaflet of the valve is frequently normal; however, the septal and posterior leaflets are deformed and may be completely fused with the endocardium of the ventricle and not attached to the annulus fibrosus.

A defect in the atrial septum is almost invariably present and may consist of an anatomically patent foramen ovale or true atrial septal defect. The thin ventricular wall of the atrialized portion of the right ventricle has been considered as an integral part of the malformation. However, this view is not definitely established, and Edwards[29] believes that the thinning may be the result of the altered dynamics that exist secondary to the deformity of the valve rather than a primary abiotrophy of the muscle tissue. The distal or functional portion of the right ventricle may reveal hypertrophy of the musculature. An excellent drawing of this anomaly is included in the article on Ebstein's anomaly by Engle and associates.[14]

The purpose of this communication is to present clinical and hemodynamic data from 4 patients with Ebstein's anomaly. Two patients represent the classical picture of the lesion in childhood. The remaining 2 patients were acyanotic adults presenting clinical features suggesting acquired heart disease. Emphasis is placed on the elements aiding in the establishment of a diagnosis in this latter group.

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This study was supported in part by U. S. Public Health Research Grant H-1208 (C2).

† Deceased, May 26, 1956.

Case Reports

Case 1. E. K. was admitted to the Pediatrics Service at Colorado General Hospital on June 7, 1949, at the age of 2 weeks because of cyanosis. The baby was the product of a normal pregnancy and an uneventful delivery and was a nonidentical twin. The fraternal twin was found to be normal in all respects. The patient was noted to be cyanotic at 5 days of age.

Physical examination revealed a well developed, well nourished baby weighing 6 lb. 14 oz., who was questionably cyanotic. The heart size was normal by palpation, and no thrills were felt. A sinus rhythm with a rate of 150 beats per minute was found. A grade I systolic murmur was heard in the third and fourth intercostal spaces at the left sternal border. The remainder of the examination was normal except for the presence of a supernumerary nipple on the right side of the abdomen.

The electrocardiogram (fig. 1) demonstrated sinus rhythm, right axis deviation, and a vertical electric position. The QRS interval was normal in duration, being 0.07 second. An R wave 11 mm. in amplitude was present in lead V_2 with an S wave of 2 mm. The intrinsicoid deflection time was 0.02 second in this lead. The tracing was interpreted as suggestive of right ventricular hypertrophy on the basis of the R-S ratio.

Roentgenologic examination (fig. 2) revealed a normal vascularity of the lung fields. There was a conspicuous concavity in the area of the main pulmonary artery segment. The right atrium was considerably enlarged, dominating the over-all cardiac silhouette. The ventricular mass appeared normal in size.

A definitive cardiac diagnosis was not established at that time and the patient was discharged. Shortly after discharge from this hospital, cyanosis was again observed by the parents and the baby was rehospitalized elsewhere for a 4-week period. On returning home, the baby gained weight very slowly and was retarded in development, lagging behind the twin both physically and mentally. Episodes of severe dyspnea associated with deep cyanosis occurred on 5 occasions during the first year of life. Profuse sweating of the head and neck was observed repeatedly throughout infancy. The child began to walk at 15 months of age and by that time showed only minimal limitation of exercise tolerance. No squatting was observed at any time.

The patient was first seen by the Cardiology Service when 25 months of age. The physical examination at that time showed no cyanosis. The heart was enlarged by palpation to the anterior axillary line in the left fifth intercostal space. A systolic thrill was palpable along the lower left sternal border. A systolic murmur was audible over the entire precordium and back, with maximum intensity at the lower left sternal border. The murmur was grade IV in intensity and blowing in quality. A protodiastolic sound was audible at the base of the heart producing a gallop rhythm. The lower border of the liver was palpable 2 cm. below the right costal margin.

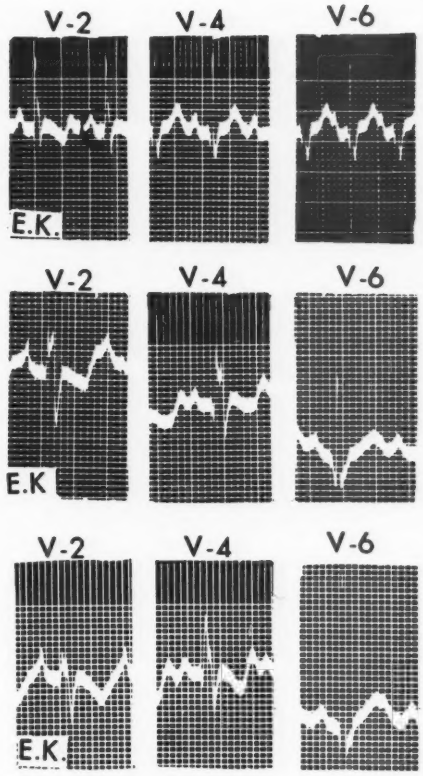

Fig. 1. Case 1. Representative precordial leads from electrocardiograms recorded at ages 2 weeks (*top*), 2 years (*middle*), and 5 years (*bottom*) demonstrate a normal QRS duration initially with subsequent widening into a pattern of right bundle-branch block. The P waves are slightly prominent at 2 weeks of age and show progressive increase in amplitude and duration with increasing age.

The electrocardiogram revealed a distinct change from the previous tracing in that the QRS interval had widened to 0.12 second with a resulting pattern of right bundle-branch block (fig. 1). The P wave had increased in amplitude in V_2.

Fluoroscopic examination revealed a decreased vascularity of the lung fields, a normal size of the right and left pulmonary arteries, and a concavity in the region of the main pulmonary artery. The right atrium was considerably enlarged. The ventricular area was also enlarged with no specific configuration (fig. 2).

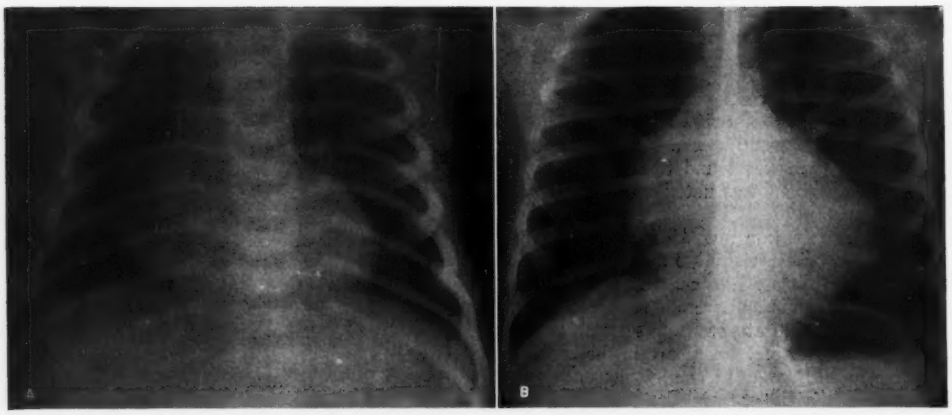

FIG. 2. *A*. Case 1. Roentgenogram at ages 2 weeks shows a prominent right atrium and an inconspicuous main pulmonary artery from the onset. *B*. Case 1. Age 5 years. This anteroposterior film shows an enlarged cardiac silhouette with a globular configuration, a narrow pedicle, and slightly decreased vascularity of the peripheral lung fields.

TABLE 1.—*Hemodynamic Data in Four Cases of Ebstein's Anomaly*

Patient	State	Pressure in mm. Hg					Blood oxygenation volumes per cent per cent saturation						Oxygen consumption ml./min.	Cardiac index L./min./M.²		Right to left-blood-shunt L./min./M.²
		Right atrium systolic/diastolic	Right ventricle systolic/early diastolic/late diastolic	Pulmonary artery systolic/diastolic	Pulmonary artery wedge mean	Brachial or femoral artery	Superior vena cava	Inferior vena cava	Right atrium	Right ventricle	Pulmonary artery	Brachial or femoral artery		Systemic	Pulmonary	
1	Rest	7/2	24/0/4	19/9	5	97/69	8.71		9.60*	9.62*		14.40	136	4.1	4.1	0
							55.0		60.5	60.8		90.9				
E. K.	Exer.	9/6				95/72						14.43				0
												91.2				
2	Rest	12/5	24/4/11	20/9		150/99	13.20	13.48	13.93			17.43	165	3.9	1.9	2.0
T. R.							58.0	59.3	61.2			76.6†				
3	Rest	10/4	29/3/13	22/10		118/69	11.21	14.11	12.09*	12.31*	12.77*	19.39	366	3.0	3.0	
							55.2	69.6	59.6	60.6	62.9	95.4				
L. B.	Exer.	13/7	28/2/10	16/3		137/75					9.49	18.11	443	2.9	2.4	0.5
											46.7	89.2†				
4	Rest	10/5	29/0/9	22/9	9	145/88					15.07	20.01	151	1.9	1.9	
											72.3	96.0				
M. P.	Exer.	11/3	40/0/9	29/8	11	160/90					9.79	17.68	390	3.0	2.3	0.7
											46.8	84.7†				

* Average of two samples.

† Pulmonary venous O_2 saturation assumed to be 95 per cent.

The child continued to be active, keeping up with the twin in all but very vigorous activities. Her weight and height remained less than the twin. Repeated examinations up to the age of 5½ years revealed a varying location and intensity of the cardiac murmurs. At one period, a loud to-and-fro murmur was audible along the left sternal border. The electrocardiographic and roentgenologic patterns remained essentially unchanged during this period (figs. 1 and 2). These clinical features suggested the presence of Ebstein's anomaly.

Cardiac catheterization was carried out when the patient was 5½ years of age (table 1). Sinus tachycardia was maintained throughout the study except for the occurrence of short runs of ventricular premature systoles on several occasions when the catheter tip lay in the right ventricle. There was no evidence of a shunt. The calculated cardiac index was within normal limits. Normal arterial oxygen saturation was present both at rest and following exercise. The right ventricular systolic pressure was normal at 24 mm. Hg. The right atrial pressure tracing

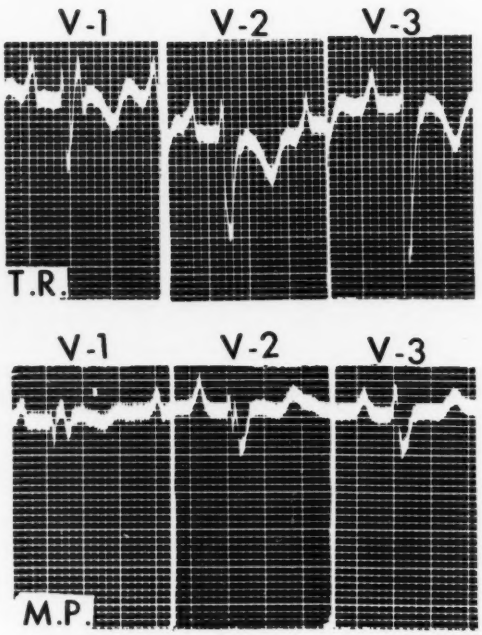

FIG. 3. Right precordial leads in case 2 (*top*) and case 4 (*bottom*) demonstrating prominent P waves and complete right bundle-branch block with low amplitude R waves.

showed a moderately prominent *a* wave. A slight pressure gradient of 5 mm. Hg was present between the right ventricle and pulmonary artery. There was moderate difficulty in introducing the catheter into the right ventricle. The point at which an atrial form of pressure wave changed to a ventricular form was observed to lie well toward the left border of the cardiac silhouette.

The catheterization data in conjunction with the clinical features were considered to establish the diagnosis of Ebstein's anomaly.

Case 2. T. R. was an 8-year-old white boy seen for the first time on May 8, 1953. He was the product of a normal pregnancy and delivery, and his growth and development were normal. The parents first noted cyanosis when he was 2 years of age. Moderate exertional dyspnea also appeared at 2 years. He was never able to keep up with other children but was able to walk half a mile at a slow pace. A doctor was first consulted when the patient was 4 years of age and the mother was informed that "something was wrong with his heart."

Physical examination showed the patient to be a well developed, well nourished boy with cyanosis of the lips and nailbeds. There was a slight bulging of the precordium, and the heart was slightly enlarged by percussion. A systolic thrill was palpable along the lower left sternal border. Auscultation revealed a harsh systolic murmur of grade IV intensity over the entire precordium with maximum intensity in the fourth and fifth left intercostal spaces parasternally. The second heart sound in the left second intercostal space was normal in intensity and pure in quality.

The electrocardiogram (fig. 3) demonstrated complete right bundle-branch block with very tall P waves in the right precordial leads, suggesting right atrial enlargement. Roentgenologic examination (fig. 4*A*) demonstrated a slightly decreased vasculature of the lung fields with small, quiet right and left pulmonary arteries. The aorta appeared normal but the main pulmonary artery was inconspicuous. The superior vena cava was seen as a prominent shadow at the base of the heart on the right. The right atrium was moderately enlarged with a considerable cephalad element to the enlargement. The right ventricular area was moderately enlarged with a fullness high along the left cardiac border. Oblique views showed that the left ventricle and left atrium were normal in size and configuration. The over-all clinical picture suggested Ebstein's anomaly.

Cardiac catheterization was performed on June 22, 1953 (table 1). The right ventricle and pulmonary artery were intubated only with difficulty, the catheter repeatedly coiling in the large right atrium. The point at which pressure contours changed from atrial to ventricular in form was observed to be far to the left of the midline, well within the usual region of the body of the right ventricle. A rather sharp angulation of the catheter course occurred on advancing the catheter through the cavity of the right ventricle and into the pulmonary artery. A paroxysmal supraventricular tachycardia with a rate of 180 beats per minute occurred during the procedure; 4 minutes after the manipulation of the catheter was stopped, it reverted to a sinus rhythm. There was no evidence of left-to-right shunt at the atrial levels. A significant right-to-left shunt was present with an estimated volume of 2.0 L. per minute. The right atrial pressure tracing initially showed prominent *a* waves averaging 12 mm. Hg in amplitude (fig. 5). During the supraventricular tachycardia, high pressure waves were recorded that were considered to represent tricuspid insufficiency. Following reestablishment of sinus rhythm, a pressure pattern of mild tricuspid insufficiency was evidenced by a pressure plateau throughout the period of ventricular systole. The right ventricular pressure tracing showed a prominent pressure wave occurring in late ventricular diastole with the same configuration and time characteristics as the *a* wave recorded in the right atrium. The systolic pressure in the right ventricle was normal, averaging 24 mm. Hg. A mild pressure gradient of 4 mm. Hg occurred between the right ventricle and pulmonary artery. The pulmonary arterial pressure wave demonstrated a variable contour. The pressure curve illustrated in figure 5, recorded in the main pulmonary artery, reveals a small

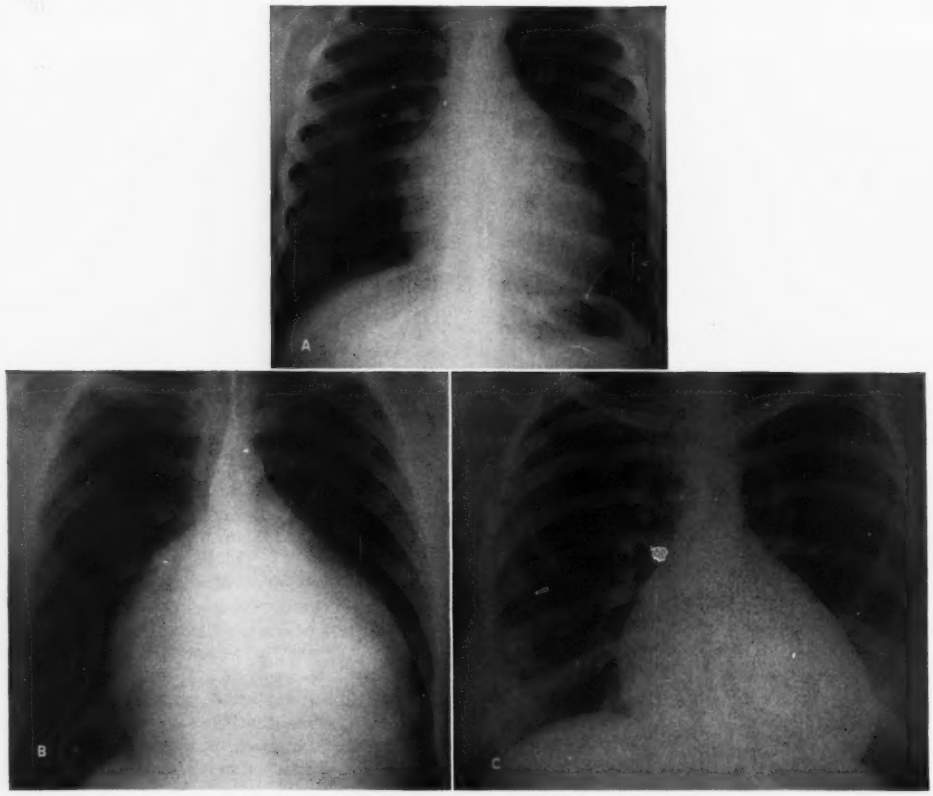

FIG. 4. Cases 2(*A*), 3(*B*) and 4(*C*). All 3 films demonstrate a prominent right atrium, a narrow pedicle with an inconspicuous main pulmonary artery, and a globular configuration to the enlarged heart.

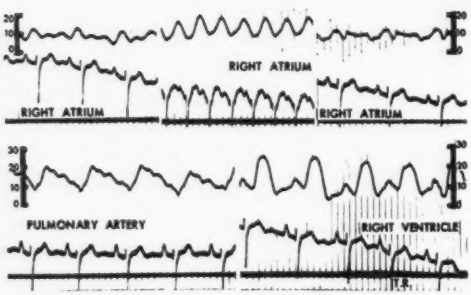

FIG. 5. Case 2. The right atrial pressure tracings show a prominent *a*-wave initially, a high wave of tricuspid insufficiency during tachycardia, and a mild pattern of residual insufficiency immediately following the tachycardia. A pressure wave occurring at the time of right atrial contraction is present in the pulmonary arterial and right ventricular tracings.

late diastolic wave coincident in timing with the *a* wave in the right atrium.

Venous angiocardiography was carried out on June 24, 1953, without incident. The study demonstrated the presence of a large right atrium in which contrast media lingered throughout the entire series. Early filling of the left atrium was evident with subsequent good filling of the left ventricle and aorta. A suggestion of a small deformed right ventricle was present. Opacification of the main pulmonary artery segment and lung fields was faint (fig. 6).

The clinical pattern and the diagnostic studies were considered clearly to confirm the diagnosis of Ebstein's anomaly.

Case 3. L. B., a 21-year-old white man, was seen at Colorado General Hospital for the first time on November 23, 1955, for evaluation of a heart murmur. This murmur was first detected during early childhood. The patient grew and developed normally and was able to keep up with companions in

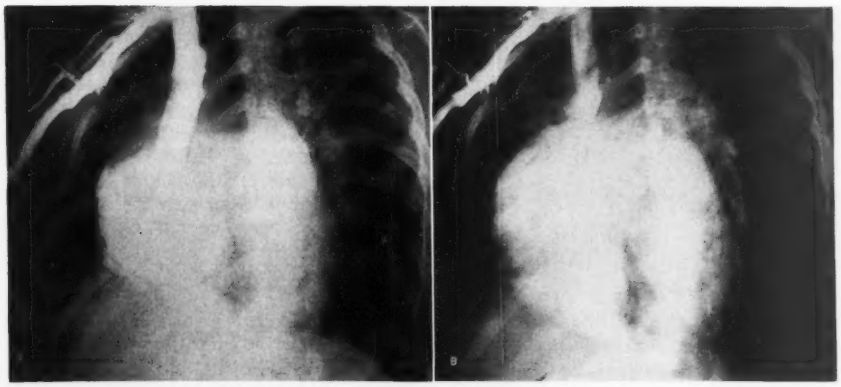

FIG. 6. *A*. Case 2. Film obtained 1 second after injection of 35 ml. of Urokon. Contrast medium is visualized in the superior vena cava and within an enlarged right atrium. Good opacification of the left atrium is noted suggesting a defect in the atrial septum. There is also suggestion of a narrow band of contrast that may reflect the displaced and malformed tricuspid valve. The lung vessels are poorly visualized. *B*. Case 2. Film obtained 5 seconds after injection reveals continued good opacification of the enlarged right atrium. The left atrium and ventricle are well opacified but the aorta is only partly visualized. The lung vessels continue to be poorly visualized. The band of contrast low in the right atrium continues to be noted.

all activities. In school he engaged in team athletics. For the past 4 years he had worked as a truck driver and loader without difficulty. He noticed exertional dyspnea only on prolonged strenuous activity. In October 1955, the patient consulted a physician because of a respiratory tract infection. A cardiac murmur was heard and the patient referred to this service for further evaluation.

Physical examination revealed a well developed, vigorous young man. A mild violaceous hue was present over the malar eminences. A presystolic venous pulsation was noted in the neck when the patient was recumbent. Palpation over the precordium revealed a diffuse cardiac thrust in the left fifth intercostal space between the midclavicular and anterior axillary lines. A faint systolic thrill was palpable at the apex. Auscultation revealed a grade IV, blowing systolic murmur at the apex that was transmitted into the left axilla. A low pitched, middiastolic murmur of grade II intensity was heard at the apex. The first heart sound in this area was accentuated. The second sound heard in the pulmonary area was diminished in intensity.

The electrocardiogram (fig. 7) showed complete right bundle-branch block. Tall, wide P waves were present in leads II, a V_F, and in the right precordial leads, indicating right atrial enlargement. Roentgenologic examination revealed a decreased vascularity in the peripheral lung fields (fig. 4*B*). The right and left pulmonary arteries were small in size and quiet in activity. The aorta was small and the main pulmonary artery was so inconspicuous as to prevent identification in the frontal view. The right atrium was markedly enlarged, projecting far to the right and superiorly. The right

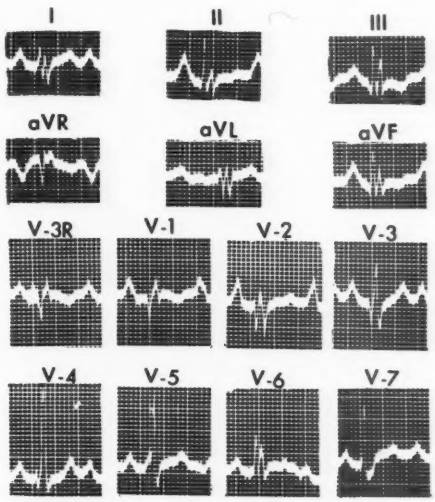

FIG. 7. Case 3. A pattern of right bundle-branch block is shown with low amplitude R waves in the right precordial leads. Tall broadened P waves are well seen in leads II, aV_F, and V_2.

ventricular area appeared considerably enlarged, filling the greater portion of the retrosternal space. A conspicuous fullness high along the left cardiac border tended to produce a globular configuration of the greatly enlarged over-all cardiac silhouette. The left heart chambers were normal.

A diagnosis of Ebstein's anomaly was made on the basis of the clinical features. Cardiac catheter-

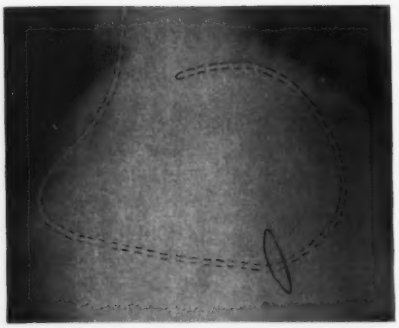

FIG. 8. Case 3. The position of the tricuspid valve as determined by a change in the pressure wave from ventricular to atrial in type is shown to lie considerably to the left of the midline.

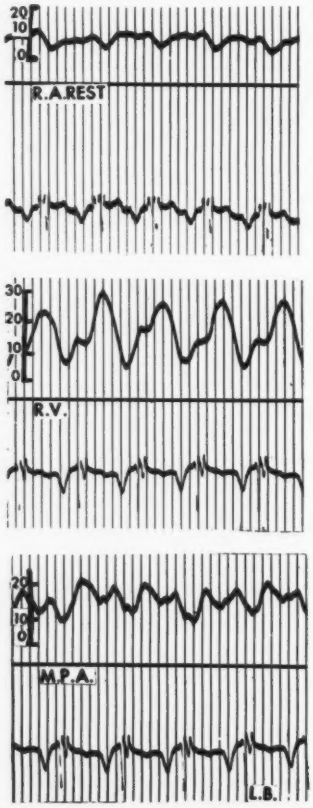

FIG. 9. Case 3. The right atrial tracing, *RA*, shows an augmented *a*-wave. The right ventricular tracing, *RV*, demonstrates a broadened and delayed right ventricular contraction wave. The pressure tracing from the main pulmonary artery shows a prominent late diastolic pressure wave.

ization was performed for evaluation of the hemodynamic status. Marked enlargement of the right atrium was demonstrated by the large diameter loop formed by the catheter as it repeatedly coiled in this chamber. The right ventricle and pulmonary artery were intubated with difficulty, the catheter being somewhat angulated when its tip lay in the pulmonary artery. The point at which right ventricular pressure pulses changed to a right atrial pressure pattern was observed well to the left of the midline (fig. 8). No shunts were demonstrable at rest. A decrease in brachial arterial oxygen saturation to 89.2 per cent following exercise was interpreted as indicating a small right-to-left shunt.

The pressure tracings from the right heart chambers are shown in figure 9. In the right atrium the *a* wave was 10 mm. Hg in amplitude at rest and 13 mm. Hg on exercise. The right ventricular pressure tracing demonstrated a high amplitude end-diastolic pressure wave resulting from right atrial contraction. The systolic pressure in the right ventricle was within normal limits and did not rise on exercise. A pressure gradient of 7 mm. Hg at rest and 12 mm. Hg on exercise was present at the pulmonic valve level. The pulmonary arterial pressure tracing showed a prominent pressure wave in late diastole that was considered to reflect right atrial contraction.

A sinus rhythm was maintained throughout the major portion of the study. Following exercise, after blood samples had been obtained and pressures determined, atrial flutter began with varying 2:1 to 4:1 block. The ventricular rate averaged 132 beats per minute. The procedure was terminated and the patient was put at bed rest. The flutter changed to atrial fibrillation at the end of 1 hour, with a ventricular rate of 86. Spontaneous conversion to a normal sinus rhythm occurred 2 hours after the onset of the arrhythmia. These data clearly confirmed the diagnosis of Ebstein's anomaly.

Case 4. Mrs. M. P., a 35-year-old white woman, was seen for the first time at Colorado General Hospital on September 2, 1954, for an evaluation of cardiac murmurs. A cardiac murmur and cardiac enlargement had first been detected 8 years previously. Since that time mild fatigue and dyspnea were noted on severe exertion. Repeated episodes of rapid heart action had occurred in the past 6 years, with rates of approximately 200 beats per minute and abrupt onset and termination. Recurrent throat infections occurred since childhood.

Physical examination revealed a well developed, well nourished woman with flushing of the malar eminences of the face. In the left lateral decubitus position a short, presystolic thrill was felt at the apex. A localized shock-like heave was palpable at the lower left sternal border. The heart was enlarged to the anterior axillary line on percussion. Auscultation revealed reduplication of the first sound in the

right second intercostal space and a grade II systolic murmur in this area. The second sound in the left second intercostal space was reduplicated and was of greater intensity than the second sound in the aortic area. The first sound at the cardiac apex was accentuated, producing a staccato quality. A second heart sound of normal intensity was present at the apex and was followed by a faint third heart sound. A low pitched, diastolic murmur with presystolic accentuation was heard immediately after the third heart sound. A grade II, blowing systolic murmur was present at the lower left sternal border. This murmur increased in intensity during inspiration.

Electrocardiography revealed a prolonged QRS interval of 0.12 second with a pattern of complete right bundle-branch block (fig. 3). High amplitude broadened P waves were present in the right precordial leads.

Roentgenologic examination (fig. 4*C*) showed the pulmonary vascularity to be normal. The right and left pulmonary arteries and the main pulmonary artery were normal in size and in amplitude of pulsation, while the aorta was small and quiet. The over-all heart size was moderately increased owing to the enlargement of the right heart chamber.

Cardiac catheterization was carried out without incident on October 19, 1954 (table 1). At the time of cardiac catheterization, the diagnosis was rheumatic heart disease with mitral and tricuspid valve involvement. Right heart chamber samples were not obtained, and the catheter position on withdrawal from the right ventricle to the right atrium was not specifically observed. Full arterial oxygen saturation was present at rest. Following exercise, moderate unsaturation to 84.7 per cent occurred. The cardiac output was significantly reduced at rest, and rose only moderately on exercise. The pressure tracing recorded in the right atrium showed prominent *a* waves with an amplitude of 10 mm. Hg (figs. 10 and 11). The right ventricular pressure tracing demonstrated a prominent late diastolic pressure wave resulting from right atrial contraction. A mild pressure gradient of 5 mm. Hg was present between the right atrium and right ventricle in early diastole, suggesting some degree of tricuspid stenosis. The peripheral pulmonary arterial pressure tracing showed a prominent secondary pressure wave in late diastole that corresponded in timing with the *a* wave of the right atrium. A systolic pressure gradient of 8 mm. Hg at rest, and 11 mm. Hg on exercise was present between the right ventricle and pulmonary artery. During exercise, prior to drawback of the catheter into the ventricle, the pressure in the pulmonary artery rose as high as 45/15 mm. Hg. Normal pulmonary arterial wedged pressure levels were recorded both at rest and with exercise.

These data obtained by cardiac catheterization failed to substantiate the diagnosis of rheumatic heart disease with mitral valve impairment. The possibility of acquired tricuspid and pulmonic valve stenosis associated with a carcinoid tumor was considered. However, a subsequent review of the entire clinical and hemodynamic pattern led to the somewhat delayed realization that all the criteria for a diagnosis of Ebstein's anomaly were fulfilled.

Discussion

Symptomatology. The symptoms associated with Ebstein's anomaly are, for the most part, nonspecific and afford little aid in establishing a diagnosis. The symptoms occurring in children with the cyanotic form of this anomaly include such general features as inadequate development and weight gain, excessive perspiration of the head and neck, and limitation of exercise tolerance. The mild degree of these symptoms with cyanosis often occurring later in childhood is of minor diagnostic value in that the most common lesion producing cyanosis in children, the tetralogy of Fallot, tends to be excluded.[14] The finding in case 2 that a cyanotic child could walk half a mile, did not squat, and had no episodes of paroxysmal dyspnea, suggested the presence of anomalies other than the tetralogy of Fallot.

The symptoms in noncyanotic patients, particularly those in the age groups where acquired valvular heart disease is common, are almost totally devoid of diagnostic significance. Relatively good exercise tolerance in the presence of considerable cardiomegaly, as in case 3, might be considered as a possible diagnostic aid.

The occurrence of paroxysmal tachycardia constitutes the single valuable feature in the symptomatology of Ebstein's anomaly.[2, 8, 9, 14-16] This symptom was a salient feature in case 4 in this series and was helpful in the establishment of the diagnosis.

The natural course of patients with this anomaly varies widely, from the occurrence of death in infancy to the maintenance of good health until late in life.[2, 17] Congestive failure may occur terminally,[2, 12] as was the case in the initial patient reported by Ebstein.[1] Death presumably due to systemic emboli may occur as a result of embolization through a defect in the atrial septum.[16, 18-21] Sudden and unexpected death is a common terminal event in patients with this lesion.[2, 16, 22, 23] The mechanism responsible for this event has been con-

sidered to be related to the paroxysmal arrhythmias characteristic of Ebstein's anomaly.

Physical Examination. The information derived by physical examination may more often be misleading than helpful in the recognition of Ebstein's anomaly. The cyanotic child constitutes a somewhat less confusing problem on examination than does the acyanotic adult, inasmuch as the diagnostic possibilities are usually limited to congenital lesions. The murmurs accompanying this lesion in the child afford the least important diagnostic information. Location, intensity, and timing of murmurs vary widely, not only from patient to patient, but at times in the same patient on serial examinations, as demonstrated in case 1.

The critical feature of the physical examination consists in the recognition that right ventricular hypertrophy is not present. This is suggested by the absence of a lift of a hypertrophied right ventricle along the lower left sternal border, and by the absence of signs of pulmonic stenosis or of pulmonary hypertension, the 2 common causes of right ventricular hypertrophy. Cyanosis in the absence of right ventricular hypertrophy should immediately suggest the possibility of Ebstein's anomaly. The physical findings in the adult with Ebstein's anomaly rarely alert the examiner to the correct diagnosis. Mild cyanosis, if present, is readily attributable to the peripheral cyanosis associated with rheumatic tricuspid valvular disease. If less common cardiac diseases are considered, the mild cyanosis may even suggest the flushing associated with carcinoid heart disease. Venous pulsations in the neck, as seen in case 3, are easily assigned to acquired tricuspid valve disease. The cardiac murmurs, present in cases 3 and 4 in this series and in many of the adults described in other series,[5, 6, 12, 24] closely mimic the murmurs of rheumatic mitral and tricuspid valve disease. The murmurs in patients with Ebstein's anomaly undoubtedly arise primarily as a result of stenosis and insufficiency of the deformed tricuspid valve. The displacement of this valve to the left explains the frequent apical location of these murmurs. The similarity of the auscultatory features of rheumatic mitral disease and Ebstein's anomaly is strikingly illustrated by the finding of an accentuated first heart sound and an opening snap at the apex in case 4. These characteristics of the heart sounds that have classically been limited to mitral valve disease can apparently arise from the tricuspid valve in Ebstein's anomaly.[12, 24]

This bewildering overlapping of signs in Ebstein's anomaly and rheumatic valvular disease permits the suggestion that a significant number of adults with this congenital anomaly are being erroneously considered examples of rheumatic heart disease.

Electrocardiography. The electrocardiogram offers valuable diagnostic aid in patients with Ebstein's anomaly. A classic feature that occurs in a high percentage of cases is complete right bundle-branch block with low amplitude R waves in the right precordial leads.[25] This form of right bundle-branch block is usually readily distinguished from that associated with severe right ventricular hypertrophy, where tall R waves are present in the right precordial leads. The characteristic configuration of the QRS complex is demonstrated in cases 2, 3, and 4 (figs. 3 and 7), and in case 1 after the age of 2 weeks (fig. 1).

A different configuration of the QRS complex occurs infrequently in patients with Ebstein's anomaly. The most common variant described is incomplete right bundle-branch block.[6, 8, 11, 12, 24-26] Complete right bundle-branch block with very tall R waves in the right precordial leads has been demonstrated in 1 case by Kjellberg and associates.[12] This very unusual pattern suggesting severe right ventricular hypertrophy was present despite a right ventricular systolic pressure of only 33 mm. Hg. The presence of free tricuspid insufficiency in this patient was considered an important element leading to the development of right ventricular hypertrophy. A right ventricular hypertrophy pattern with a normal QRS interval represents an additional unusual variation from the classic electrocardiogram. Evidence of right ventricular hypertrophy with a normal QRS duration is present in the right precordial leads in case 3 of Brown and associates.[26] A normal QRS duration is demonstrated in case 2 in the present series at 2 weeks of age (fig. 1) with an R-S ratio suggesting right ventricular hypertro-

phy.[27] Normal ventricular conduction time with no evidence of right ventricular hypertrophy was found in case 1 in the series reported by Broadbent and associates.[9] Further unusual patterns include incomplete bundle-branch block of indeterminate type as seen in case 4 of Brown,[26] and complete left bundle-branch block as described by Adams and Hudson.[17]

The occurrence of these variant forms of QRS complexes permits a reconstruction of the development of the classic pattern of complete right bundle-branch block. The finding of normal conduction and intermediate degrees of incomplete block suggests that the conduction impairment is not an intrinsic element of the anomaly caused by a defect in the conduction system itself, but is a result of changes in structure of the right ventricle due to the physiologic stress imposed by the tricuspid valve deformity.[2, 28] The serial tracings from case 1 (fig. 1) offer conclusive evidence that intraventricular conduction may be normal shortly after birth and be progressively lengthened with increasing age. It is postulated that the right bundle-branch block arises as a result of the dilatation and thinning of the atrialized proximal portion of the right ventricle. Normal conduction or partial degrees of right bundle-branch block may be present at an early age or in milder forms of the anomaly where this portion of the right ventricle is less markedly dilated.

Right ventricular hypertrophy is a disconcerting feature that considerably diminishes the diagnostic value of the electrocardiogram when present. Hypertrophy of the right ventricle has seldom been described at postmortem examination. However, hypertrophy of the distal portion of the right ventricle was described by Brown and associates in 2 patients, 1 of whom demonstrated electrocardiographic evidence of right ventricular hypertrophy.[26] Inasmuch as a normal right ventricular pressure and a normal or decreased right ventricular output is the invariable physiologic pattern in this anomaly, it is difficult to account for this occasional right ventricular hypertrophy. A possible explanation is that the functioning portion of the right ventricle constitutes only a fraction of the total right ventricular mass and therefore is subject to a relative increase in work load in relation to a normal output. Evidence of severe right ventricular hypertrophy must be ascribed to other types of physiologic stress such as the marked tricuspid insufficiency present in the patient described by Kjellberg.[12]

The occasional finding of left bundle-branch block is considered a manifestation of an associated cardiac lesion. Coronary atherosclerosis may well have been responsible for this phenomenon in the elderly patient described by Adams and Hudson.[17]

The P-wave abnormalities are an equally consistent feature of the electrocardiogram in Ebstein's anomaly.[25] Tall, broadened P waves characteristically occur in precordial leads overlying the right atrium and in the limb leads, reflecting the potential developed in this chamber. The increased amplitude of these P waves is clear evidence of hypertrophy of the right atrium. The broadened duration of these P waves frequently results in prolongation of the PR interval. The broadening and slurring of the P waves can be interpreted as reflecting dilatation of this chamber with consequent delay in conduction.

An additional electrocardiographic feature of Ebstein's anomaly is the occurrence of supraventricular arrhythmias. These may consist of paroxysmal atrial or nodal tachycardias and occasionally atrial flutter or fibrillation (case 3).[7, 13, 25, 28]

Roentgenography. Fluoroscopic examination of the patient with Ebstein's anomaly offers the most specific diagnostic evidence that can be obtained by the simpler methods of evaluation. A characteristic pattern is present that frequently will permit the establishment of a definitive diagnosis.[22] Enlargement of the right atrium is the dominant radiologic feature in Ebstein's anomaly. The first film in the series, shown in figure 2, shows a very prominent right atrium in a 2-week-old infant. This prominence of the right atrium in case 1 progressed with increasing age. The right atrium enlarges anteriorly, encroaching on the retrosternal area, and also develops in a cephalad direction, elevating the point of juncture with the ascending aorta. The right ventricle is also

enlarged and shows a rounded configuration with low amplitude pulsations. Bulging of the right ventricular outflow tract frequently produces a prominence high along the left cardiac border,[6, 12] a finding demonstrated in all patients in this series (figs. 2 and 4). The protrusion of the distal portion of the deformed right ventricle that is responsible for this roentgenologic configuration is well illustrated by Edwards.[29]

The pulmonary arterial pattern is also characteristic on fluoroscopy. The main pulmonary artery is small and in conjunction with the dilated right ventricle immediately below may be scarcely detectable in the frontal view (fig. 4). The right and left pulmonary arteries are usually small and show small amplitude pulsations. The vascularity of the lung fields may appear normal or decreased, depending on the magnitude of the right-to-left shunt. The aorta is typically small and inactive.[14, 30]

The over-all pattern produced by these features is an enlarged, quiet heart with a globular configuration and a narrow pedicle usually accompanied by decreased vascularity of the lung fields. This pattern is generally distinctive from that of the tetralogy of Fallot or of isolated valvular pulmonic stenosis, 2 congenital lesions often confused with Ebstein's anomaly. The differential diagnosis in adults must include consideration of acquired tricuspid valve disease and pericardial effusion.[14, 26]

Angiocardiography has proved a useful diagnostic aid in this anomaly.[4, 12-14, 18] The usual elements noted following injection of contrast material are a voluminous right atrium that remains opacified for a prolonged period, prompt filling of the left atrium through a patent foramen ovale in the cyanotic patient, a deformed right ventricular chamber situated well toward the left heart border, and poor visualization of the main and peripheral pulmonary arteries.

Cardiac Catheterization. Ebstein's anomaly has been established as a clinical entity largely as a result of information derived by cardiac catheterization. This diagnostic procedure continues to be the most effective means of confirming the presence of this anomaly. The emphasis on serious complications accompanying cardiac catheterization in the initial reports[14, 18] has not been substantiated in the more recent reports of larger numbers of patients.[11, 12, 26] The arrhythmias occurring in cases 2 and 3 in this series were no more significant than similar arrhythmias occurring during cardiac catheterization in patients with other forms of congenital cardiac anomalies.

The principal diagnostic features on cardiac catheterization consist of a greatly enlarged right atrium, displacement of the tricuspid valve to the left, normal right ventricular, pulmonary arterial and pulmonary arterial wedge pressure, and absence of an arteriovenous shunt. These elements in a cyanotic patient are conclusively diagnostic. In an acyanotic adult considered to have rheumatic valvular disease, the hemodynamic pattern should reveal the diagnostic error. However, cardiac catheterization will not be diagnostic of Ebstein's anomaly unless the clinician includes this congenital defect in the precatheterization differential diagnosis.

The specific details of the pressure phenomena recorded in the right heart chambers and pulmonary arterial system are of minor diagnostic value. They are of considerable value, however, in leading to an understanding of the altered hemodynamics associated with this unusual form of congenital heart disease. The result of contraction of the enlarged right atrium influences the pressure patterns obtained at all levels. An elevated mean pressure with a prominent *a* wave is the usual pattern recorded in the right atrium. This accentuated *a* wave reflecting hypertrophy of the right atrium can be considered to result from an impedance to normal emptying of the right atrium due to the small volume of the distal portion of the right ventricle, and to possible minor degrees of tricuspid stenosis. A pressure pattern of tricuspid insufficiency may occur less commonly in the right atrium.[9, 10] Free tricuspid insufficiency is demonstrated in the right atrial pressure tracing presented by Gøtzsche and Falholt,[11] and by Kjellberg and associates.[12] The series of right atrial pressure curves in figure 5 show the development of tricuspid insufficiency during tachycardia with

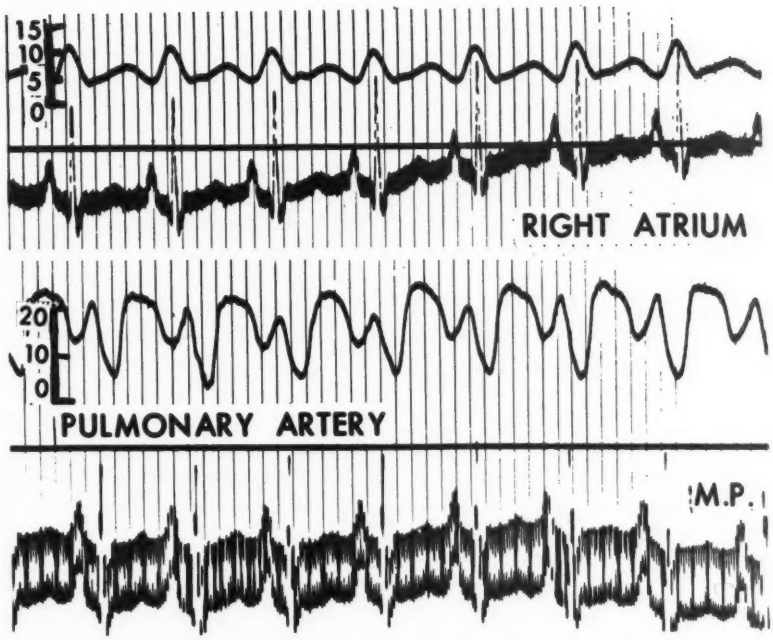

FIG. 10. Case 4. The right atrial pressure tracing shows an accentuated *a* wave. The pulmonary arterial tracing shows a bizarre, bifid wave with the secondary peak occurring at the time of right atrial contraction.

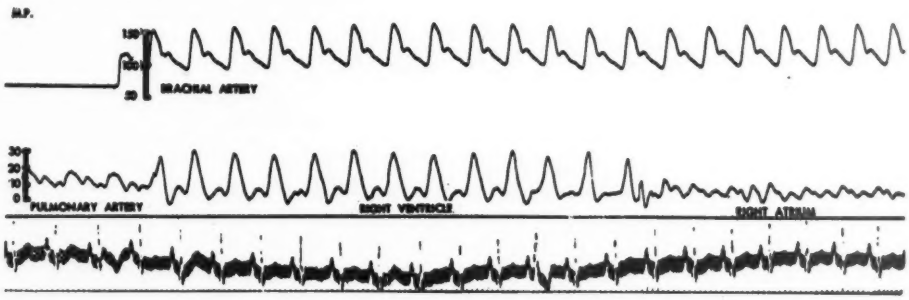

FIG. 11. Case 4. A continuous pressure tracing shows a systolic pressure gradient at the pulmonic valve level and a mild early diastolic pressure gradient at the tricuspid valve level.

a mild residual insufficiency following the arrhythmia.

The right ventricular pressure curves are characterized by normal systolic, normal early diastolic, and high end-diastolic levels. The high late diastolic pressure wave can be identified by its temporal relations and magnitude as resulting from right atrial contraction. This transmission of the pressure wave attending right atrial contraction to the right ventricle is illustrated in figures 5 and 10, and in the pressure tracings presented by Medd, Mathews, and Thursfield.[24] It is reasonable to assume that this forceful end-diastolic filling is a significant aid in effecting maximum filling of the small distal portion of the right ventricle, and thereby assures maximum output from this chamber. A mild pressure gradient is present between the right atrium and right ventricle in early diastole in the pressure trac-

ing in case 4 (fig. 11) indicating a mild degree of tricuspid stenosis. The form of the right ventricular ejection wave itself is abnormal with widening, delay in onset, and delay in reaching a peak. This may reflect the abnormal electric activation of the right ventricle.

A systolic pressure gradient is frequently present between the right ventricle and pulmonary artery (fig. 11). This evidence of mild obstruction to right ventricular outflow was noted in all the present cases and in many of the cases previously reported.[11,12] Postmortem studies of the heart in Ebstein's anomaly seldom reveal actual pulmonic valve stenosis. This obstruction, therefore, is probably a manifestation of a hypoplastic pulmonic valve ring and pulmonary artery. The occurrence of pulmonary hypertension during exercise in case 4, with a normal pulmonary arterial wedge pressure is a further suggestion that the pulmonary arterial system is decreased in capacity.

The pulmonary arterial pressure tracings demonstrate an unusual series of pressure waves that vary considerably in configuration in different regions of the pulmonary arterial system. It is possible to identify a pressure wave with temporal relationships similar or identical to those of the augmented *a* wave in the right atrium (figs. 9–11). Similar right atrial pressure activity was described by Blacket and co-workers[6] in the pulmonary arterial pressure tracing of a patient with Ebstein's anomaly. The presence of right atrial pressure activity superimposed on pulmonary arterial tracings,[31] and even systemic arterial tracings[32] has been noted in other forms of cardiac disease. A comparison of the pressure levels in the pulmonary artery and in the right atrium at the time of right atrial contraction in end-diastole shows that the right atrial pressure may equal or exceed that in the pulmonary artery at that phase of the cardiac cycle. This pressure relationship suggests that right atrial contraction may affect pulmonary arterial filling and contribute in some degree to the propulsion of blood into the pulmonary arterial system.[6] This phenomenon would assign to the right atrium the role of an accessory right ventricle.

Therapy. A satisfactory surgical procedure has not as yet been developed for correction of the cardiac defect in Ebstein's anomaly. This situation is readily understandable in view of the nature of the basic abnormality, consisting as it does of an inadequate propulsive force generated by the deformed right ventricle. Direct manipulation of the deformed tricuspid valve, even with the ample open operative period afforded by present technics, would not appear to be a fruitful approach to the correction of this anomaly.

Two types of palliative surgical procedures have been performed in patients with Ebstein's anomaly. The first of these is the Blalock-Taussig anastomosis. This procedure theoretically offers the possibility of palliation in patients with right-to-left shunts of large volume through an atrial communication. This method thus utilizes the left ventricle as a partial substitute for the ineffective right ventricle to achieve a more normal pulmonary blood flow. Despite the theoretical benefit to be derived from a Blalock-Taussig anastomosis, its application in patients with Ebstein's anomaly has been unrewarding. Operative fatality has occurred in all instances, regardless of whether the correct diagnosis was established preoperatively,[8] or whether the erroneous diagnosis of a tetralogy of Fallot[14, 28] was made.

A second type of palliative surgical procedure consists of closure of the communication between the 2 atria. This has been accomplished in a 25-year-old man with Ebstein's anomaly, reported by Wright and associates,[10] with relief of cyanosis and improvement in exercise tolerance. As the authors point out, if nothing else, the procedure results in the elimination of the right-to-left shunt with its attendant hazard of thromboembolic disease from paradoxical emboli or from the secondary polycythemia. In addition to this benefit, the closure of this outlet to right atrial outflow may result in an increased right atrial pressure and consequent enhancement of the role of the right atrium as an accessory right ventricle. This possible benefit from an increased right atrial pressure might, however, be achieved only at the price of hastening the onset of con-

gestive failure. Operative fatality associated with closure of an atrial defect has been mentioned in 2 patients with Ebstein's anomaly[33] since this initial successful case of Wright.

Operative intervention has not been recommended in any of the 4 patients reported here.

Summary

Four cases of Ebstein's anomaly are presented that demonstrate the characteristic clinical and hemodynamic features of this congenital cardiac defect. Two of these patients were acyanotic adults who presented auscultatory findings closely resembling those of acquired mitral and tricuspid valve disease. It is suggested that a significant number of patients with Ebstein's anomaly are mistakenly considered to have rheumatic valvular heart disease.

Summario in Interlingua

Es presentate quatro casos del anomalia de Ebstein que exhibi le characteristic aspectos clinic e hemodynamic de iste congenite defecto cardiac. Duo del patientes esseva adultos acyanotic qui presentava constatationes auscultatori multo simile a illos de acquirite morbo de valvula mitral e tricuspide. Es stipulate que un numero significative de patientes con anomalia de Ebstein es erroneemente considerate como affligite de rheumatic morbo de valvula cardiac.

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ing in case 4 (fig. 11) indicating a mild degree of tricuspid stenosis. The form of the right ventricular ejection wave itself is abnormal with widening, delay in onset, and delay in reaching a peak. This may reflect the abnormal electric activation of the right ventricle.

A systolic pressure gradient is frequently present between the right ventricle and pulmonary artery (fig. 11). This evidence of mild obstruction to right ventricular outflow was noted in all the present cases and in many of the cases previously reported.[11,12] Postmortem studies of the heart in Ebstein's anomaly seldom reveal actual pulmonic valve stenosis. This obstruction, therefore, is probably a manifestation of a hypoplastic pulmonic valve ring and pulmonary artery. The occurrence of pulmonary hypertension during exercise in case 4, with a normal pulmonary arterial wedge pressure is a further suggestion that the pulmonary arterial system is decreased in capacity.

The pulmonary arterial pressure tracings demonstrate an unusual series of pressure waves that vary considerably in configuration in different regions of the pulmonary arterial system. It is possible to identify a pressure wave with temporal relationships similar or identical to those of the augmented *a* wave in the right atrium (figs. 9–11). Similar right atrial pressure activity was described by Blacket and co-workers[6] in the pulmonary arterial pressure tracing of a patient with Ebstein's anomaly. The presence of right atrial pressure activity superimposed on pulmonary arterial tracings,[31] and even systemic arterial tracings[32] has been noted in other forms of cardiac disease. A comparison of the pressure levels in the pulmonary artery and in the right atrium at the time of right atrial contraction in end-diastole shows that the right atrial pressure may equal or exceed that in the pulmonary artery at that phase of the cardiac cycle. This pressure relationship suggests that right atrial contraction may affect pulmonary arterial filling and contribute in some degree to the propulsion of blood into the pulmonary arterial system.[6] This phenomenon would assign to the right atrium the role of an accessory right ventricle.

Therapy. A satisfactory surgical procedure has not as yet been developed for correction of the cardiac defect in Ebstein's anomaly. This situation is readily understandable in view of the nature of the basic abnormality, consisting as it does of an inadequate propulsive force generated by the deformed right ventricle. Direct manipulation of the deformed tricuspid valve, even with the ample open operative period afforded by present technics, would not appear to be a fruitful approach to the correction of this anomaly.

Two types of palliative surgical procedures have been performed in patients with Ebstein's anomaly. The first of these is the Blalock-Taussig anastomosis. This procedure theoretically offers the possibility of palliation in patients with right-to-left shunts of large volume through an atrial communication. This method thus utilizes the left ventricle as a partial substitute for the ineffective right ventricle to achieve a more normal pulmonary blood flow. Despite the theoretical benefit to be derived from a Blalock-Taussig anastomosis, its application in patients with Ebstein's anomaly has been unrewarding. Operative fatality has occurred in all instances, regardless of whether the correct diagnosis was established preoperatively,[8] or whether the erroneous diagnosis of a tetralogy of Fallot[14, 28] was made.

A second type of palliative surgical procedure consists of closure of the communication between the 2 atria. This has been accomplished in a 25-year-old man with Ebstein's anomaly, reported by Wright and associates,[10] with relief of cyanosis and improvement in exercise tolerance. As the authors point out, if nothing else, the procedure results in the elimination of the right-to-left shunt with its attendant hazard of thromboembolic disease from paradoxical emboli or from the secondary polycythemia. In addition to this benefit, the closure of this outlet to right atrial outflow may result in an increased right atrial pressure and consequent enhancement of the role of the right atrium as an accessory right ventricle. This possible benefit from an increased right atrial pressure might, however, be achieved only at the price of hastening the onset of con-

gestive failure. Operative fatality associated with closure of an atrial defect has been mentioned in 2 patients with Ebstein's anomaly[33] since this initial successful case of Wright.

Operative intervention has not been recommended in any of the 4 patients reported here.

Summary

Four cases of Ebstein's anomaly are presented that demonstrate the characteristic clinical and hemodynamic features of this congenital cardiac defect. Two of these patients were acyanotic adults who presented auscultatory findings closely resembling those of acquired mitral and tricuspid valve disease. It is suggested that a significant number of patients with Ebstein's anomaly are mistakenly considered to have rheumatic valvular heart disease.

Summario in Interlingua

Es presentate quatro casos del anomalia de Ebstein que exhibi le characteristic aspectos clinic e hemodynamic de iste congenite defecto cardiac. Duo del patientes esseva adultos acyanotic qui presentava constatationes auscultatori multo simile a illos de acquirite morbo de valvula mitral e tricuspide. Es stipulate que un numero significative de patientes con anomalia de Ebstein es erroneemente considerate como affligite de rheumatic morbo de valvula cardiac.

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Okita, G. T., Talso, P. J., Curry, J. H., Jr., Smith, F. D., Jr., and Geiling, E. M. K.: Metabolic Fate of Radioactive Digitoxin in Human Subjects. J. Pharmacol. & Exper. Therap. **115:** 371 (Dec.), 1955.

Biosynthetically labeled C^{14}-digitoxin was administered intravenously in multiple doses to 3 terminal patients. The various tissue samples at autopsy were assayed for both the unchanged drug and its metabolic products. The myocardium does not have any special affinity for the cardiac glycoside in comparison to other organs. On a tissue-weight basis, the kidney, gallbladder contents, and entire intestines have the highest concentration of unchanged digitoxin, whereas the spleen, jejunal contents, and gallbladder contents have the highest concentration of metabolic products. On a whole organ basis, the liver has the largest amount of both digitoxin and its metabolic products. The hypothetic scheme of the possible course of events based on the results is as follows: After its intravenous administration, there is a rapid initial removal from the vascular system as evidenced by the disappearance of approximately 60 per cent of drug from the blood stream within 15 min. after its administration. During this period, as well as after the digitoxin blood level has reached equilibrium, some of the drug is metabolized by the liver and both the glycoside and its metabolic products enter the gastrointestinal tract via the biliary route. A major portion of the metabolites and some of the unchanged digitoxin are then reabsorbed by the small intestine and enter the enterohepatic cycle. With this passage, small amounts of the metabolic products and lesser amounts of the unchanged drug are continuously removed from the vascular system by the kidney. This accounts for the greater excretion of the drug and metabolites by way of the kidneys than by way of the feces.

Aviado

Effect of Prolonged Steroid Therapy for Rheumatic Fever on the Exchangeable Potassium Content and Body Weight

By JERRY K. AIKAWA, M.D.

With the technical assistance of Aaron J. Blumberg

Serial measurements of the body weight and exchangeable potassium content were made in 13 children with acute rheumatic fever who were being treated with large doses of corticotropin or cortisone. In 8 subjects the clinical signs of hyperadrenalism developed. Seven of the 13 subjects showed at least a 20 per cent increase in body weight, which could not be explained on the basis of changes in the body's exchangeable potassium content. This weight gain is thought to be due to an increase in total body fat.

THE prolonged administration of cortisone or corticotropin (ACTH) in therapeutic doses produces the physical signs of hyperadrenalism. Previous studies have demonstrated that the increase in body weight resulting from such therapy in rheumatic children cannot be accounted for solely on the basis of retention and redistribution of sodium and water, since the variations in the exchangeable sodium content of the body do not parallel the changes in body weight.[1] The results of these studies suggested that the change in body composition might be due to an increase in fat; however, the possibility of an increase in total muscle mass as a cause of the weight gain could not be completely excluded.

The purpose of the present study on rheumatic children was to investigate further the nature of the alterations in body composition and weight during the prolonged administration of cortisone or long-acting corticotropin (in the form of Acthar gel). Radioactive potassium (K^{42}) was used for this investigation.

MATERIAL AND METHODS

Subjects. Thirteen hospitalized children, 9 boys and 4 girls, with the diagnosis of acute rheumatic fever were studied. Their ages ranged from 5 to 15 years. All showed unequivocal clinical symptoms and signs of acute rheumatic activity, as judged by the diagnostic criteria of Jones.[2]

The general plan of therapy was to administer cortisone in a daily dosage of 5.5 to 9.4 mg./Kg. of initial body weight. In 10 of the 12 patients treated according to this plan, the initial dosage of cortisone ranged between 6.1 and 7.9 mg./Kg. One patient (case 7, table 1) was treated with corticotropin, starting with a dose of 2.3 units/Kg. These dosages of cortisone or corticotropin were maintained until the clinical and laboratory evidences of rheumatic activity had subsided, at which time they were gradually reduced. If signs of rheumatic activity recurred, the dosage was increased to an intermediate level until all evidences of activity had again subsided. The longest duration of continuous cortisone therapy was 124 days and the shortest, 57 days. Acthar gel was administered for 119 days in case 7.

All patients were placed on a regular hospital diet and received supplemental feedings between meals as desired. All received oral supplements of potassium as chloride or citrate, 2 to 3 Gm. daily.

Isotopes. Isotopic potassium (K^{42})* was prepared for injection in the manner previously described,[3] in sterile physiologic saline solution.

Determination of Exchangeable Potassium Content (K_e). Each subject received an intravenous injection of radioactive potassium (1.5 μc./Kg. of body weight) between 8:30 and 10 a.m. All urine voided thereafter until 6 a.m. the following day was collected, and the K^{42} content of the pooled specimen was determined. Determinations of the specific activity were made on 3 spot samples of urine obtained at 7, 8, and 9 a.m. the day after injection.

The mathematical calculation of the value for the

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This study was supported in part by a grant-in-aid from the American Heart Association and in part under a contract with the U. S. Atomic Energy Commission.

Dr. Aikawa is an Established Investigator of the American Heart Association.

* K^{42} was supplied by the Oak Ridge National Laboratory, Oak Ridge, Tenn., on allocation from the U. S. Atomic Energy Commission.

TABLE 1.—*Clinical and Laboratory Findings During Cortisone and Corticotropin Therapy of Rheumatic Fever*

Case	Age (yr.) and sex	Initial weight (Kg.)	Cortisone			Duration of therapy (days)	Signs of hyperadrenalism	Days of therapy	Change in wt. (Kg.)	Exchangeable K		Serum concentration (mEq./L.)	
			Maximum dose (mg./day)	Initial dose (mg./Kg.)	Total dose (Gm.)					K_e (mEq.)	K_e/wt. (mEq./Kg.)	Na	K
1	9 M	26.4	200	7.6	13.65	110	+	13	+0.9	1191	43.6	142.6	4.9
								27	+1.3	1003	36.2	132.3	5.0
								41	+6.3	1185	36.2	145.6	5.3
								69	+8.8	1367	38.8	147.7	4.7
								84	+10.4	1388	37.7	144.6	4.2
2	6 M	20.6	135	6.6	9.53	83	+	3	−0.5	780	38.8	150.3	4.5
								45	+6.1	1157	43.3	141.1	4.5
								59	+7.7	1208	42.7	151.7	4.6
								87	+7.9	1103	38.7	151.6	4.2
								102	+7.0	984	35.7	147.9	4.7
3	11 M	27.5	200	7.3	10.08	63	+	8	+1.0	1314	46.1	149.3	5.6
								22	+1.9	1269	43.1	136.2	4.6
								50	+7.2	1267	36.5	147.7	3.7
								65	+8.9	1361	37.5	146.2	4.1
4	15 M	68.2	375	5.5	17.85	87	+	75	+10.9	2873	36.3	150.9	3.9
								102	+12.7	2284	28.2	143.9	4.7
5	10 F	31.0	200	6.5	18.63	105	+	4	+0.1	1220	39.2	148.2	3.9
								45	+6.2	1219	32.8	148.6	4.6
								59	+8.2	1266	32.3	145.6	3.7
								87	+12.3	1395	32.3	141.5	3.8
								102	+15.6	1404	30.1	147.0	3.9
6	5 M	15.9	150	9.4	6.43	59	+	11	+1.4	915	52.9	149.1	5.2
								39	+3.2	713	37.3	146.1	4.6
								53	+3.6	728	37.3	152.5	4.5
7	14 F	43.6	100*	2.3	6359*	119	+	58	+7.8	2045	39.8	151.2	4.0
								86	+12.3	1634	29.2	144.8	4.3
								100	+13.2	1814	31.9	151.6	4.6
								128	+18.2	1979	32.0	145.7	4.0
								156	+17.3	2091	34.3	153.0	4.4
8	12 M	37.1	250	6.7	11.08	63	+	41	+5.5	1873	43.9	147.8	4.3
								69	+6.7	1287	29.4	141.1	4.3
9	13 F	54.1	350	6.5	21.90	62	0	6	+0.4	1598	29.3	139.2	3.8
								34	+2.2	1660	29.5	140.8	4.6
10	8 F	19.1	150	7.9	13.28	124	0	3	−2.6	614	33.0	147.8	4.9
								16	+4.7	647	32.4	156.0	5.1
								44	+4.7	835	41.8	153.3	4.6
								72	+2.1	745	38.2	142.1	4.4
								100	+12.0	791	37.0	142.0	4.4
11	6 M	18.0	120	6.7	6.06	58	0	20	+2.1	963	47.9	150.6	4.3
								34	+2.1	954	47.5	141.6	5.7
								62	+3.0	889	42.4	138.6	4.6
								77	+2.2	879	43.5	144.6	4.4
12	12 M	32.7	200	6.1	9.58	102	0	83	+8.7	1214	29.3	142.9	4.3
								97	+9.6	1787	42.2	154.7	4.7
								103	+11.8	1750	39.3	140.3	4.3
								117	+10.5	1811	41.9	147.9	4.4
13	8 M	27.3	175	6.4	6.50	57	0	36	+4.1	1410	44.9	153.7	4.1
								58	+5.0	1376	43.1	146.3	4.6

* Dosage of Acthar gel (units).

exchangeable potassium content of the body has been described in detail previously.[3, 4]

Preliminary studies in this laboratory confirmed the observations of Corsa and his associates[4] that the specific activity of potassium in the urine of both diseased and normal subjects reaches an equilibrium within 18 hours. The mean difference in specific activity among the 3 spot specimens, when expressed as percentage of the mean K_e, was 4.57 ± 2.76 per cent. In another group of 11 hospitalized subjects who were in a steady state, 2 K_e determinations made in this laboratory within a period of 2 weeks agreed within a mean of 2.12 ± 1.10 per cent.

The total number of determinations of exchangeable potassium content was 48; a minimum of 2 and a maximum of 5 serial determinations were performed on each subject, usually at intervals of 2 to 4 weeks. Each patient was observed for a minimum of 65 days.

Measurement of Radioactivity. The radioactivity of the urine was determined with a well-type scintillation counter and a scaling circuit. A total of 10,000 counts were made on each sample. All determinations were corrected for physical decay of the isotope. Sodium and potassium concentrations in the serum, and potassium concentration in the urine were determined with a Baird flame photometer, by the lithium internal standard method.

Results

The results are presented in table 1.

Signs of Hyperadrenalism. Eight of the 13 subjects (cases 1 to 8) showed obvious clinical signs of hyperadrenalism—moon face, cervical and supraclavicular fat pads (buffalo hump), and acne—while being treated with cortisone or corticotropin. In the other 5 subjects (cases 9 to 13) some fullness of the face developed but there were no other obvious manifestations. If the length of hospital stay gives any indication, there was no relationship between the development of hyperadrenalism and the therapeutic effectiveness of the drug: in the group of patients with marked hyperadrenalism the mean duration of hospitalization was 104 days (range, 75 to 140), whereas in the group with mild signs the mean duration was 96 days (range, 65 to 124).

Changes in Body Weight. In 12 of the 13 subjects (all except case 9) the body weight increased by at least 10 per cent. In 7 of these patients (cases 1, 2, 3, 5, 6, 7, and 12) the weight gain was more than 20 per cent of the initial value. The greatest increase was observed in a girl (case 5) who showed a steady gain in weight to a maximum of 50 per cent of the initial value on the one hundred and second day of cortisone therapy. In 1 patient treated with corticotropin (case 7) the weight gain was similar to that seen in most of the children given cortisone. One girl (case 9) failed to gain weight, although she showed some fullness of the face.

Although there was considerable variability, the increase in body weight appeared to be progressive and related to the duration of therapy (fig. 1). No definite relationship was observed between the changes in body weight and the therapeutic effectiveness of cortisone or corticotropin. The mean duration of hospitalization in those subjects whose weight

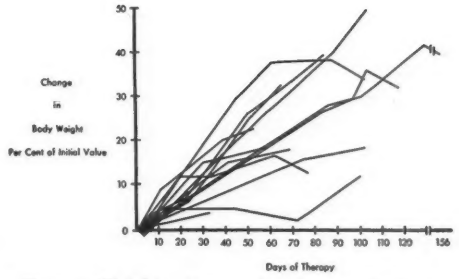

Fig. 1. Weight changes in rheumatic subjects treated with cortisone or corticotropin.

Table 2.—*Summary of Clinical and Laboratory Findings During Steroid Therapy of Acute Rheumatic Fever*

Case	Signs of hyperadrenalism	Weight gain >20% initial wt.	Decrease in K_e/wt. >5 mEq./Kg.	Change in K_e		
				>15% initial value	<15% initial value	No change
1	+	×	×	×		
2	+	×	×	×		
3	+	×	×			×
4	+		×		×	
5	+	×	×	×		
6	+	×	×		×	
7*	+	×	×			×
8	+		×		×	
9						×
10				×		
11						×
12		×		×		
13						×

* Treated with corticotropin. All other patients treated with cortisone.

gain amounted to more than 20 per cent of the initial body weight was 110 days (range, 75 to 140), whereas the mean duration in those subjects whose weight gain was less than 20 per cent of the initial body weight was 91 days (range, 65 to 124).

Changes in Exchangeable Potassium Content (K_e). With 1 exception (case 12) all initial values for exchangeable potassium content, when related to body weight, were within the range previously established for normal adult men and women.[5, 6] Data of a similar nature for normal children are not yet available.

In the 8 patients who had definite clinical evidences of hyperadrenalism the value for K_e/wt. showed a rather consistent decrease, which was proportional to the duration of therapy with cortisone or corticotropin. In every instance the final value for K_e/wt. was at least 5 mEq./Kg. lower than at least 1 of the previous values obtained in the same patient. Furthermore, the decrease in the value for K_e/wt. was accompanied in every instance by an increase in total body weight. There was, however, no consistent pattern of change in the *absolute* values for K_e. While 2 subjects (cases 3 and 7) showed no significant change between the initial and final values of K_e, 3 (cases 1, 2, and 5) showed an increase of 15 per cent or more and 3 (cases 4, 6, and 8) showed a decrease of 15 per cent or more.

The 5 patients in whom no overt clinical manifestations of hyperadrenalism developed did not show a definite pattern of change in the values for K_e/wt. In 1 subject (case 9) the K_e was observed for less than 40 days after the initiation of cortisone therapy, and showed no change; this was the only patient whose weight did not increase by more than 10 per cent of the initial value. She was relatively obese prior to therapy and remained so during the period of observation. The other girl in this group (case 10) showed an increase in K_e and K_e/wt. during therapy, the final values on the hundredth day being 29 per cent and 4 mEq./Kg. higher than the respective initial values. In the 3 boys (cases 11, 12, and 13) the values for K_e/wt. were in the range of 42 to 44 mEq./Kg.; except for case 12, serial determinations of the values for K_e and K_e/wt. showed no significant changes.

Changes in Serum Electrolyte Concentration. Except for 1 determination each in cases 1 and 10, all values for serum sodium were within the normal range of 135 to 155 mEq./Kg. All values for serum potassium were within the normal range of 3.5 to 5.5 mEq./Kg.

Discussion

The prolonged administration of large doses of cortisone or corticotropin to rheumatic subjects may produce clinical manifestations of hyperadrenalism, which are usually associated with an increase in body weight. Since it has been previously demonstrated that this weight gain is greater than could be accounted for by changes in the exchangeable sodium content of the body,[1] it is presumed that some explanation other than retention of sodium and water must be sought.

Because corticotropin was used exclusively in the previous study, it was not known whether the changes in weight and exchangeable sodium content were due specifically to the corticotropin or to a contaminant of the Acthar gel, such as pitressin. Since similar changes have been observed in the present study with cortisone, the possibility of a contaminant does not appear likely.

There is the possibility that the initial catabolic effect of corticotropin or cortisone on protein metabolism may be reversed by prolonged administration, so that an increase in muscle mass is responsible for the weight gain. It has been previously demonstrated that positive nitrogen balance may be attained during steroid therapy, provided the dietary intake is great enough.[7] Such an anabolic process should result in an increase in the exchangeable body potassium content, since muscle mass would be increased. It is evident that under the circumstances of the present study the total body content of potassium did not show a consistent increase while a patient is receiving large doses of cortisone or corticotropin. In fact, 3 of the 13 subjects showed a decrease in K_e, and 5 showed no appreciable change. Hence, the anabolic effect *per se* cannot explain all of the

changes in body weight, nor can they explain the clinical manifestations of hyperadrenalism.

It is highly unlikely that the weight gain is due to an increase in the intracellular content of water and electrolytes, and in osmolarity, or in both, without an associated increase in the intracellular sodium content. Such an intracellular water increase can occur only in the presence of a positive balance of potassium and the data show no consistent trend in this direction.

The data from the present study confirm the clinical impression that prolonged therapy with corticotropin or cortisone may produce an excessive accumulation of body fat. This may result from a specific effect on fat metabolism, or may reflect an increase in appetite and food intake. In favor of the former interpretation is the observation that carcasses of rats treated with corticotropin, when compared with those of controls on the same food intake, show a relative and absolute increase in fat content.[8] On the other hand, children and adolescents on cortisone or corticotropin therapy do have enormous appetites.

The signs of hyperadrenalism produced by the prolonged administration of relatively large doses of cortisone or corticotropin resemble those of spontaneous Cushing's syndrome. In the latter condition, deposits of fat, most conspicuous in the face, neck, and trunk, have been demonstrated by histologic means.[9] Although no direct evidences supporting this hypothesis can be found in this or the previous study,[1] it appears most likely that the changes in body weight and in the exchangeable sodium and potassium contents can be attributed largely to an accumulation of body fat.

Summary

Serial measurements of the body weight and exchangeable potassium content (K_e) were made in 13 children with acute rheumatic fever—1 who was being treated with long acting corticotropin and 12 who were being treated with cortisone in daily doses ranging initially from 5.5 to 9.4 mg./Kg. of body weight.

All but 1 subject showed at least a 10 per cent increase in body weight. Eight manifested the typical clinical signs of hyperadrenalism. In all of these 8 subjects the values for K_e/wt. decreased during therapy, suggesting that the increase in body weight was due to a change in body composition. The fact that no consistent change in K_e was observed indicates that the increase in body weight was not due solely to an increase in muscle mass.

The results demonstrated that the change in body composition observed during the prolonged therapy of rheumatic fever with cortisone or corticotropin is characterized by a relative decrease in the potassium as well as the sodium content of the body. It is suggested that the total fat content of the body may have been increased.

Summario in Interlingua

Esseva facite mesurationes del peso corporee e del contento de kalium excambiabile (K_e) in 13 juveniles con acute febre rheumatic—1 qui esseva tractate con corticotropina e 12 qui esseva tractate con cortisona in doses diurne de (initialmente) inter 5,5 e 9,4 mg per kg de peso corporee.

Omne le subjectos, con un exception, monstrava al minus 10 pro cento de augmento de peso corporee. Octo manifestava le typic signos clinic de hyperadrenalismo. In omne iste 8 subjectos, le proportion K_e/peso descresceva durante le therapia. Isto suggereva que le augmento del peso corporee esseva debite a un alteration in le composition del corpore. Le facto que nulle systematic alteration del K_e esseva observate indica que le augmento del peso corporee non esseva exclusivemente debite a un augmento del massa muscular.

Le resultatos demonstra que le alteration del composition corporee observate durante le prolongate therapia de febre rheumatic con cortisona o corticotropina es characterisate per un relative reduction del contento de kalium e etiam de natrium in le corpore. Nos opina que le contento total de grassia in le corpore esseva possibilemente augmentate.

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Waterman, D. H., Samson, P. C., and Bailey, C. P.: The Surgery of Patent Ductus Arteriosus. Dis. Chest **29:** 102 (Jan.), 1956.

Analysis of 3,896 patent ductus operations by 49 cooperating surgeons is presented. Of these, 2,929 operations were performed in children and 967 in adults.

The data show a sharp upswing in the 2 most significant preoperative symptoms, myocardial insufficiency and infection, between the children and the adults. The over-all operative mortality was 2.77 per cent (children 2.3 per cent; adults 5.5 per cent). The clinical results in the survivors was considered satisfactory in 98.3 per cent of the children and 95.5 per cent of the adults.

In response to 4 specific questions, the following was ascertained:

1. *Surgical Technic.* The majority of the investigators favored division of the duct as opposed to ligation. There was no difference in mortality, however, between the 2 series.

2. *Pulmonary Hypertension.* In regard to ductal interruption in the presence of pulmonary hypertension, opinion was overwhelming that it should be done.

3. *Reversal of Shunt.* When the shunt has reversed from a predominantly left-to-right flow to a right-to-left one, most surgeons opposed surgery. Some investigators, however, thought that if the pulmonary artery pressure fell after temporary clamping, the duct should be divided.

4. *Absence of Cardiac Enlargement and Symptomatology.* All but 1 of the surgeons favored ductal interruption in the absence of cardiac enlargement or clinical symptomatology.

Supplementary data, from a more limited group of surgeons, revealed: most previously enlarged hearts decreased to normal size after surgery; 7.1 per cent of cases had a coexistent aneurysm (ductus, pulmonary artery, or aorta); hemorrhage at operation was the largest single cause of death.

The committee concluded that the operation is a standardized and safe procedure, that the finding of a patent ductus, in the absence of a right-to-left shunt, is a definite indication for surgery, and that the operation is optimally performed during childhood.

MAXWELL

Pressor Effects of Norepinephrine After Drastic Reduction of Sodium Intake

By L. K. DAHL, M.D.

The mechanisms whereby dietary sodium restriction leads to decreased arterial blood pressure is obscure. Previously reported studies of patients with arterial hypertension showed a lessened pressor response to norepinephrine after sodium restriction. In the present investigations, reduction in pressor response to norepinephrine during the low sodium period was observed only occasionally; sodium restriction decreases blood pressure in some hypertensive patients by other unknown mechanisms.

THE present study was undertaken to confirm the report of Raab, Humphreys, Makous, DeGrandpré, and Gigee[1] that sodium restriction in hypertensive patients resulted in abolition or significant diminution of the pressor response to norepinephrine. For some years the author has been interested in the mechanism by which sodium limitation lowers the blood pressure in about a quarter to one third of patients with so-called "essential" hypertension. Therefore he was prepared to accept the conclusions of the work above as a possible partial explanation for the phenomenon.

In the studies reported here, 8 hypertensive adults, as well as a normotensive individual who served as a control subject, were studied on an otherwise constant diet before and after marked curtailment of sodium intake under carefully controlled conditions on a metabolic ward. Under these circumstances it was found that the pressor response to norepinephrine after reduction of sodium intake decreased infrequently enough to raise serious doubts whether this may be regarded as an important mechanism by which a low-sodium regimen affects hypertension.

MATERIAL

The pertinent clinical and laboratory data on these 9 patients are summarized in table 1. All 8 of the individuals with hypertension had uncomplicated disease, with no history of edema, cardiac failure, cerebrovascular accidents, or antecedent renal disease. In 7 the diagnosis of "essential" hypertension seems highly probable; the eighth, a woman of 64 (patient S) whose blood pressure had reached normal levels by the end of the 8-week control period before sodium restriction, probably had an arteriosclerotic component of some degree. Patient L, an obese woman of 55, also had mild, asymptomatic diabetes. The hypertensive patients had negative phentolamine (Regitine) tests for pheochromocytoma and intravenous pyelograms were within normal limits in all. The nonhypertensive man of 55 had classical, active, rheumatoid arthritis of about 2 years' duration and gave no history or signs suggestive of cardiovascular disease. He underwent precisely the same regimen as the others for a 14-week period. Since the primary purpose of this communication is not concerned with the clinical effects of sodium restriction in hypertension, reported frequently in the past,[2-5] complete clinical and laboratory data have been included only where necessary.

METHOD

Diet. On admission all patients were placed on a palatable low-sodium diet accurately calculated and weighed daily with an intake of approximately 5 mEq. (115 mg.) sodium per day (5.3 ± 0.95 mEq. by analysis of 62 daily diets). Restriction of sodium to this amount allowed 45 to 55 Gm. of protein per day in the food; the protein intake was therefore supplemented with the low sodium protein foods Lesofac* or Lonalac to give a total of 1.5 Gm. of protein per Kg. body weight per day. The patients were required to eat salt-free or salt-poor carbohydrates and fats in amounts sufficient to satisfy appetite and maintain admission weight. During the first 5 to 8 weeks of hospitalization, 10 Gm. (170 mEq.) of enteric coated NaCl were taken daily; at the end of this control period, the NaCl was removed—the sole change in regimen—and the patient was then maintained on the basic low sodium regimen until discharge, approximately 3 months after admission. Because of the palatability of this diet and the indoctrination of the patients, surreptitious ingestion of salt did not occur on this regimen, as con-

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This work was carried out under the auspices of the Atomic Energy Commission.

*Obtained through the courtesy of Wyeth Laboratories, Philadelphia, Pa.

TABLE 1.—*Pertinent Clinical and Laboratory Data*

Patient	Hol.	B	C	D	G	H (colored)	K	L	S
Hosp. no.	6901	7159	6950	7094	6431	6495	6825	7135	6865
Diagnosis	Rheumatoid arthritis	EHT*	EHT	EHT	EHT	EHT	EHT	EHT	?EHT
Age	55	47	45	38	64	54	52	55	64
Sex	♂	♂	♀	♀	♀	♀	♀	♀	♀
Height (cm.)	172	179	157	151	147	158	160	152	154
Weight (Kg.)†	77.4	71.0	87.0	46.4	64.4	71.3	81.3	82.6	57.4
Known duration of hypertension (Yrs.)	—	2	0.5	7	30	5	11	16	2
Blood pressure (mean & S.D.)									
on High Na^+‡	114 (3)	194 (15)	188 (13)	213 (15)	182 (24)	207 (11)	190 (19)	197 (13)	148 (12)
	70 (3)	114 (7)	95 (6)	124 (9)	91 (12)	108 (6)	90 (9)	103 (8)	81 (9)
on Low Na^+‡	116 (12)	162 (10)	172 (17)	147 (9)	140 (12)	143 (10)	141 (19)	163 (9)	124 (6)
	69 (4)	98 (5)	83 (10)	94 (10)	71 (4)	84 (7)	73 (8)	92 (5)	75 (6)
Heart size (x-ray)§	Enlargement Sl. general	Normal	Enlargement Sl. general	Normal	Enlargement Mod. general	Enlargement increased width	Enlargement "Considerable" generalized	Diffuse aortic widening	Normal
Electrocardiogram§	Normal	L.V.H.	"Probably normal"	L. Vent. hypertrophy	Nonspecific T-wave changes	Nonspecific T-wave changes	L. Vent. hypertrophy and strain	Low T waves	Normal
Renal function§									
Albuminuria	0	0	0	0	0	0	0	0	0
Urea clearance (% Normal)	104	71	89	92	73	102	80	53	84
BUN (mg. %)	10	15	9	15	21	11	15	17	14
Disease other than hypertension	0	0	Psoriasis	0	0	0	0	Mild diabetes (found at BNL)	Otosclerosis (± 30 yrs)

* Essential hypertension.
† Last day of high Na^+ period.
‡ Average of last 10 days on high and low Na^+ periods, respectively.
§ During high Na^+ phase.

firmed by analysis of all 24-hour urines for sodium throughout the period of hospitalization.

Hospital Regimen. The patients were ambulatory throughout their stay except for several hours during certain studies, or for intercurrent illnesses. Patients were weighed daily, nude, after voiding, and before breakfast. Blood pressures were measured 6 mornings a week under standard conditions by the author or an associate.

Experimental Procedure. Experiments were done in a quiet air-conditioned room at 72 F. with the patients usually nonfasting, in bed, and horizontal. The studies were made after equilibration had occurred on both the high and low sodium phases (table 2) of the regimen. Through a 3-way stopcock, either 5 per cent dextrose in water or norepinephrine (Levophed) 4 mg. base per L. were infused into the left antecubital vein. The flow rate of norepinephrine was controlled precisely by a Bowman constant infusion pump; although the flow rates for this instrument had been calibrated before the onset of this entire series of infusions, after each separate experiment it was recalibrated for the specific flow rates used and the doses were calculated accordingly. For each patient, identical doses of norepinephrine (γ/Kg./min.) were the aim during both phases of the study; slightly different dose rates resulted in some individuals, however, as shown in table 3. Blood pressures were measured in the right arm with systolic and diastolic pressures recorded as the first appearance and total disappearance of sound respectively.[6] During the first 15 to 30 minutes, which made up the control period, 5 per cent dextrose solution was infused at about 10 to 15 drops per minute and blood pressures were recorded at 1- to 4-minute intervals until a reproducible basal level was reached that usually was similar to the current morning readings. When this stable level was attained, norepinephrine was substituted for the 5 per cent dextrose.

During the high sodium phase, when individual sensitivity—and hence pressor response—to norepinephrine was unknown, the initial dose rates approximated .05 γ/Kg./min. Infusions were continued for 10 to 40 minutes at a single level until it was clearly evident either that no pressor response had occurred or until a new level of blood pressure had become stabilized. At this point, either the norepinephrine was stopped and the blood pressure allowed to return to basal levels before proceeding to the next larger dose (if the previous pressor response had not been too great) or the dose-rate was increased immediately: repeated checks indicated that the fina levels reached were the same by either method, hence the second became the routine.

The average of the last 3 (occasionally 4) blood pressure recordings in any period was used to compute the pressures shown in table 3. The spread among these readings was small as shown by a standard deviation of only ±4.36 and ±2.72 mm. Hg for systolic and diastolic respectively in the entire series.

TABLE 2.—*Time Relationships Between l-Norepinephrine Studies and Na Restriction*

Patient & Dx	Hospital day				
	Begin high Na^+	N.E. study I*	Begin low Na^+	N.E. study II†	End low Na^+
Hol (R.A.)‡	1	30	41	91	101
B (EHT)§	1	18	50	95	100
C(EHT)	1	35	47	91	101
D(EHT)	1	23	50	95	109
G(EHT)	1	47	55	82	95
H(EHT)	1	46	55	80	95
K(EHT)	1	34	47	93	101
L(EHT)	1	22	50	95	106
S(?EHT)	1	34	54	92	101

* and † Norepinephrine study before and after Na restriction, respectively.

‡ Rheumatoid arthritis.

§ Essential hypertension.

RESULTS

The results are summarized in table 3. In columns 4 to 8 the systolic and diastolic pressor responses to norepinephrine are shown, both in absolute (mm. Hg) and relative (per cent of basal pressure) terms. Only 1 patient (C) demonstrated a clear-cut decrease in sensitivity at all dose levels in both systolic ($p < .02$) and diastolic ($p < .05$) pressures. Several of the other patients had similar effects, although less constantly (D, L, S). When the pressor responses are projected as percentile increases of the basal pressures (columns 5 and 8), some of the barely significant ($p < .05$) absolute declines become insignificant or actually suggest *enhanced* sensitivity (patient H). There appeared to be no clear-cut relationship between change in sensitivity, degree of hypertension, or diminution in basal pressure following NaCl restriction. For instance, patients C and K had roughly comparable disease: C had an insignificant fall in blood pressure after sodium limitation but had a significant decline in pressor response to the drug; K had a significant drop in systolic pressure with an equivocal decrease in pressor response. Patients D and H both had a highly significant drop in pressure with salt restriction; but D had a decreased systolic pressor response and H probably had an in-

TABLE 3.—*Pressor Effects of L-norepinephrine Before and After NaCl Restriction*

Patient and Dx	L-norepinephrine (γ/Kg./min.)	Systolic B.P.			Diastolic B.P.		
		B.P. (mm.Hg)	Abs. ↑ (mm. Hg)	% ↑	B.P. (mm. Hg)	Abs. ↑ (mm. Hg)	% ↑
1	2	3	4	5	6	7	8
Hol. ♂	†*Before* (B)						
55	0.0	105‡			65		
Rheumatoid arthritis	.058	115	10	10	70	5	8
	.101	138	33	31	87	12	18
	†*After* (A)						
	0.0	105			68		
	.051	112	7	7	73	5	7
	.099	128	*23*§	22	80	12	18
B ♂	B						
47	0.0	158			107		
EHT*	.058	168	10	6	108	1	1
	.097	185	25	16	117	10	9
	.169	205	47	30	125	18	17
	A						
	0.0	153			110		
	.057	175	*22*	14	120	*10*	9
	.097	172	19	12	122	12	11
	.166	203	50	33	128	18	16
C ♀	B						
45	0.0	194			93		
EHT	.047	215	21	11	102	9	10
	.084	220	26	13	100	7	7
	.143	240	46	24	103	10	11
	A						
	0.0	198			97		
	.045	197	*−1*‖	−1	97	*0*	0
	.090	195	*−3*	−2	95	*−2*	−2
	.157	205	*7*	4	97	*0*	0
D ♀	B						
39	0.0	200			133		
EHT	.100	272	52	24	143	10	8
	A						
	0.0	143			93		
	.087	162	*19*	13	105	12	13
G ♀	B						
64	0.0	168			80		
EHT	.069	208	40	24	93	13	16
	A						
	0.0	145			75		
	.071	184	39	27	88	13	17
H ♀	B						
54	0.0	213			108		
EHT	.073	235	22	10	122	14	13
	.11	253	40	19	128	20	19
	.19	270	57	27	122	14	13
	A						
	0.0	137			83		
	.080	148	*11*	8	93	10	12
	.14	175	38	28	97	*14*	17
	.23	193	56	41	100	17	20
K ♀	B						
52	0.0	183			85		

TABLE 3—*Continued*

Patient and Dx	L-norepinephrine (γ/Kg./min.)	Systolic B.P.			Diastolic B.P.		
		B.P. (mm. Hg)	Abs. ↑ (mm. Hg)	% ↑	B.P. (mm.Hg)	Abs. ↑ (mm. Hg)	% ↑
1	2	3	4	5	6	7	8
EHT	.054	231	48	26	101	16	19
	A						
	0.0	148			77		
	.058	188	40	27	83	*6*	8
L ♀	B						
55	0.0	203			100		
EHT	.052	233	30	15	113	13	13
	.088	245	42	21	107	7	7
	A						
	0.0	178			112		
	.050	198	*20*	11	113	*1*	1
	.085	207	*29*	16	118	6	5
S ♀	B						
64	0.0	145			88		
PEHT	.075	170	25	17	98	10	11
	.129	221	76	52	109	21	24
	A						
	0.0	120			82		
	.086	148	28	23	87	*5*	6
	.142	165	*45*	38	93	*11*	13

* Essential hypertension.

† Before and after Na restriction, respectively.

‡ Differences in mean B.P. for all patients between tables 1 and 3 are partly explained on longer Na restriction for averages in table 1. However, for patient B, mean B.P. shown in table 3 is lower than table 1: the presumed explanation is the much longer basal period of measurement in norepinephrine test in a patient with labile hypertension.

§ Different from corresponding *Before* dose by >1 standard deviation ($p < .05$).

‖ Different from corresponding *Before* dose by >2 standard deviations ($p < .02$).

creased systolic pressor effect after norepinephrine. Relative to his initial pressure, normotensive patient Hol. responded in a fashion similar to that of some of the hypertensive patients, both before and after decreasing his salt intake.

DISCUSSION

It is apparent that the results reported here do not confirm previous evidence of a uniform reduction in pressor effectiveness of norepinephrine after NaCl limitation.[1] In an attempt to explain the discrepancy, some of the following factors bear consideration although, since the clinical data on the 4 cases previously reported are limited, comparisons between the 2 groups of patients are difficult. 1. The slightly lower sodium content of the diet in the current investigation (115 mg. versus 180 mg./day) is an unlikely source of the disparity. 2. It is possible that by chance, hypertensive patients were selected, all of whom responded in the fashion reported by Raab and associates.[1] The writer, for instance, recently had 7 hypertensive patients on this low sodium regimen, 6 of whom responded with highly significant ($p < .01$) declines in both systolic and diastolic levels—a fortuitously high number of responses. 3. The control studies in the earlier report apparently were made while the patients were on a more or less unrestricted diet, following which the rice-fruit diet was begun, and 10 to 30 days later the effect of sodium withdrawal on norepinephrine sensitivity was tested. Since the rice-fruit diet is low both in NaCl as well as in protein,[4] metabolic adjustments were required, not only for salt restriction, but for the probably more complex phenomena associated with attaining nitrogen equilibrium at the lowered level of protein intake. It was found by Dole

and co-workers[4] that of 6 hypertensive subjects who were studied under metabolic ward conditions for 6 months, only 1 patient—the smallest—attained positive nitrogen balance 3 months after going on the rice-fruit diet. Therefore, while the major compensatory reaction to salt restriction may have been completed within the 10 to 30 days following institution of the new diet, it is highly unlikely that the subjects were in positive nitrogen balance. This supposition is rendered likely by the fact that 2 of the 3 patients had steadily declining weights on the rice-fruit diet (weights were not reported in the fourth subject). In the series presently reported, the only dietary change throughout the entire period of study was the withdrawal of the daily sodium chloride supplement of 10 Gm. during the low-sodium phase of the study.

While these are offered as possible explanations for the discrepancies between the 2 sets of experimental results, it should be conceded that there may exist other, and more plausible, explanations. It seems fair to conclude, however, that drastic limitation of sodium itself may be, but commonly is not, followed by a decreased pressor response to norepinephrine.

Summary

Studies on 9 adults, 8 of whom were hypertensive, failed to confirm the previous report of a uniform decrease in pressor response to norepinephrine following sodium withdrawal. Several possible explanations were proposed to explain the disparity between the 2 sets of data.

Summario in Interlingua

Studios in 9 adultos, 8 del quales esseva hypertensive, non confirmava le previe reporto de un uniforme reduction del responsa pressorial a norepinephrina post abstention ab natrium. Plure explicationes possibile es proponite pro explicar le disparitate inter le duo series de datos.

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We must not forget that the physician above all should keep in mind the welfare of his patient, his constantly changing state, not only in the visible signs of his illness, but also in his state of mind, which must necessarily be an important factor in the success of the treatment. One would be blind not to recognize that before and even after the advent of modern scientific medicine there were great and able healers of the sick who were not men of science, but who had the ability to reassure the patient and thus favourably to influence the course of illness. It is also obvious that there have been excellent scientists who were very mediocre practitioners.—Arturo Castiglioni, 1874–

Thrombotic Obliteration of the Branches of the Aortic Arch

By ROBERT B. KALMANSOHN, M.D., AND RICHARD W. KALMANSOHN, M.D.

This report presents the sixth case of thrombotic obliteration of the branches of the aortic arch to be documented in this country. The world's literature on this subject is reviewed and analyzed from the standpoints of clinical characteristics, etiology, and pathology.

PULSELESS disease, or Takayashu's disease, is an unusual syndrome characterized by the obliteration of the major branches of the arch of the aorta. The name, pulseless disease, does not appear to be adequate, for it fails to indicate the peculiar localization of the disease and the clinical variants with diminished, but present pulses. The name Takayashu's disease is subject to the criticism usually voiced against eponyms; further, Takayashu described only the ocular manifestations of this condition.[1] In addition, this syndrome was adequately documented by Broadbent[2] 33 years prior to Takayashu's description. The most appropriate nomenclature is considered to be thrombotic obliteration or thromboangiitis obliterans of the branches of the aortic arch because of the consistent demonstration of intravascular clot formation (thrombus), of inflammation of the vessel wall (angiitis), and of the peculiar anatomic localization (aortic arch). Furthermore, this name implies an appropriate lack of knowledge of specific etiology.

Although 90 cases have been reported of this condition to the present time,[1, 3-7] only 5 reports have originated in the United States.[4, 5-7] This report presents the sixth case to be documented in this country and a comprehensive review on this subject.

CASE REPORT

M.B., a 41-year-old white woman, was first seen on November 5, 1955, with the chief complaint of dizziness of 10 years' duration.

Present Illness. The patient stated that she was apparently well until about 1945, when she noted the onset of dizziness; this sensation consisted of subjective vertigo and occurred chiefly on change in position or on walking along the street at a moderate pace. The symptom was slowly progressive in frequency and duration. During the 3 months prior to entry, she had 2 episodes of loss of consciousness while walking, without aura, vomiting, convulsions, or tongue biting. For about 6 months she noted weakness of all her extremities with fatigue that necessitated complete rest of the involved extremities. Over this same time cramps in the shoulders and hands occurred, particularly when knitting or writing, severe enough to make her discontinue these activities.

She was troubled with almost constant tingling and numbness of the fingers and toes for about 3 years, more pronounced on the right. For the same time she was aware of some thinning of the facial muscles and easy fatigue of the muscles of mastication; accordingly, she learned to eat slower and to eliminate gum chewing. The patient was unaware of any ocular or mental abnormalities.

Past History. The patient had the usual childhood diseases, an appendectomy in 1922, and a kidney suspension in 1945. At that time she was first told that the blood pressure could not be obtained in the upper extremities. A hysterectomy was performed for uterine fibroids in 1945. There was no history of unexplained fevers, venereal disease, or other illnesses other than respiratory illnesses.

She smoked 10 cigarettes a day, but denied any intake of alcoholic beverages. The system history was noncontributory.

Physical Examination. The patient was asthenic but in no apparent discomfort. There was marked atrophy of all the facial muscles, and forced mastication resulted in fatigue with claudication. There was no nystagmus, strabismus, or corneal opacity; the arteriolar light reflex was increased and there were no hemorrhages, exudates, papilledema, or vascular anastomoses. There were no other abnormalities of the eyes, ears, nose, or throat. No goiter was palpated. The lungs were clear. The heart rate was 84 and regular and the left heart border was at the midclavicular line in the fifth interspace. The sounds were audible without murmurs, gallops, or rubs; A_2 was greater than P_2. The abdomen was not remark-

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able, the reflexes were physiologic, and no lymph nodes were palpated. Rectal and pelvic examination were normal except for mild cervicitis.

Pulses were not palpated in the radial, ulnar, brachial, subclavian, innominate, right common carotid, or right and left temporal arteries. There was a weak pulsation in the left common carotid artery and minimal pressure over it resulted in syncope. There were no thrills, murmurs, or bruits in the neck. All the pulses in the lower extremities were palpable, but weak; the abdominal aorta was also weakly palpable. The blood pressure in the legs was 150/90. As would be expected, there were no oscillometric deflections in the upper extremities and less than a 1-point deflection in the neck. The skin and appendages of the extremities were not atrophied and skin temperature felt normal.

Laboratory Examination. The erythrocyte sedimentation rate was 8 mm. per hour (Wintrobe). The white blood count was 10,050 and 19,800 per mm.; the differential count was 59 per cent polymorphonuclear leukocytes, 43 per cent lymphocytes, 2 per cent eosinophils, and 5 per cent monocytes. The hemoglobin was 10.5 Gm. per cent. Serologic test for syphilis was negative. Urinalysis showed a specific gravity of 1.015 and negative albumin, sugar, and microscopic examinations. The lupus erythematosus preparation was negative and a biopsy of the gastrocnemius muscle was normal.

Agglutinations for typhoid, paratyphoid, proteus OX 19, and *Brucella abortus* were negative. The total protein was 5.8 Gm. per cent with 4.5 Gm. of albumin. An electrocardiogram showed incomplete right bundle-branch block. A ballistocardiogram* displayed cut-off K waves. Skin tests were negative for histoplasmin and P.P.D. no. 1 and positive for P.P.D. no. 2 and coccidiodin 1/100.

The patient was referred back to her family physician with the advice that she be maintained on anticoagulant therapy.

Historical Aspects

Although there have been many case reports of absent pulses in the upper extremities due to syphilitic aneurysms,[8-11] these cases do not logically belong within the scope of this paper because of their different etiology. In 1875, Broadbent[2] described a 50-year-old man with absent radial pulses and a history of syphilis in whom no aneurysm was found at postmortem examination. The patient did have extensive atheromata with calcification and complete obliteration of the great vessels; endarteritis obliterans was present histologically. No subsequent description of this condition was forthcoming until the much quoted report by Takayashu, a Japanese ophthalmologist, in 1908.[1] He described the ocular manifestations, particularly emphasizing the peripapillary anastomoses. He had no postmortem confirmation, but correctly hypothesized occlusion of the great vessels of the arch of the aorta. In the following years, several cases of this condition were reported in the Japanese literature almost exclusively by ophthalmologists without pathologic confirmation.[1, 12, 13] Case reports also appeared outside of Japan under various titles.[14, 15] Interest in this disease received its biggest impetus when Shimizu reviewed the literature in 1951 and coined the catchy phrase "pulseless disease"[1]; Shimizu's account received wide recognition and was abstracted in the J. A. M. A. in 1951.[16]

The first account of this condition to appear in the American literature was by Giffin and associates of the Mayo Clinic in 1939.[7] He correctly alluded to this condition as a reversed coarctation with symptoms of a brain tumor. His patient was a 19-year-old white girl. The second case report from the United States was in 1954 by Caccamise and Whiteman,[4] also of a 19-year-old white girl. Two additional cases were reported from the United States in 1953 in a complete review of the aortic arch syndrome: one in a 33-year-old Indian woman, the other, in a 45-year-old white man. The etiology was obscure in both patients.[5] In 1955, a second case of aortic arch syndrome was reported from the Mayo Clinic,[6] in a 64-year-old white woman; this patient died of a subendocardial myocardial infarction. At postmortem examination the entire thoracic aorta, as well as the branches of the arch of the aorta were involved with a chronic inflammatory reaction; the coronary arteries were patent, but the ostia were narrowed by a nonatheromatous deposition of connective tissue in the intima of the aorta. Although this patient's age was unusual for this condition, her pulses may have been absent for many years without clinical recognition. The pertinent data of the cases reported until this time in the American literature are summarized in table 1.

* Ballistocardiograph (Photoelectric), Sanborn Company, Cambridge, Mass.

TABLE 1.—*Review of All Patients with Pulseless Disease Reported in the United States*

Age	Sex	Chief complaint	Laboratory findings	Remarks	Author—Date
1. 19	female	headaches, failing vision	not remarkable	visual claudication	Giffin, Dry, Horton 1939.[7]
2. 19	female	syncope, amblyopia	not remarkable	bilateral amblyopia	Caccamise and Whitman 1952.[4]
3. 45	male	dizziness, black spots before eyes	WBC 9000; sedimentation rate 8 mm./hour	13-year interval from trauma to symptoms	Ross and McKusick 1953.[5]
4. 33	female	angina pectoris	not remarkable	aorta a calcified tube on surgical exploration	Ross and McKusick 1953.[5]
5. 64	female	chest pain	WBC 4600; sedimentation rate 75 mm./hour	chronic inflammation of thoracic aorta	Barker and Edwards 1955.[6]
6. 41	female	dizziness	WBC 10,050, 19,800; sedimentation rate 8 mm./hour	marked facial atrophy	Kalmansohn, 1957

In 1954 Erik Ask-Upmark[3] reviewed the world's literature, excluding Japan, of 28 recorded cases, including 2 of his own. Of necessity we have drawn heavily on the material presented in this paper.

CLINICAL DESCRIPTION

Age. The age at onset in those cases reported outside of Japan varied from 11 to 64, with an average of 19; the diagnosis was usually made about the age of 31. The first knowledge of absent pulses in our patient was at the age of 29.

Sex. As has been noted by others,[1, 3, 4] this disease tends to affect young women. In the Japanese series 45 out of 50 cases where sex was mentioned were female; in the cases reported outside of Japan, all but 2 have been female, one exception being a case report from Great Britain by Skipper and Flint in 1953,[15] and the second, a 45-year-old white man from the United States.[5] This strong predilection for the female sex has been a factor in helping to eliminate such diseases as arteriosclerosis and thromboangiitis obliterans. The reason for this preponderance has not been elucidated; there has been no evidence of endocrine disease in those instances in which it has been looked for.[3]

Incidence. The frequency of this disease is difficult to estimate; 90 cases have been documented in the world's literature. However, it is doubtful that only 6 cases have existed in this country, 5 of which were recorded in the last 4 years. Since the preparation of this paper, I have been told of another case in the United States that was not published. It is hoped that the present review will increase clinical awareness of this condition.

Geographic Distribution. As already indicated, 58 cases have been reported from Japan; the 32 cases outside of Japan have the following geographic distribution: Sweden 10, United States 6, Great Britain 5, Norway 3, Hungary 2, and 1 case each from Germany, France, Roumania, Greece, Switzerland, and Spain. We think that these figures do not reflect the true geographic incidence of the disease.

Symptoms and Signs. The symptoms and signs of this disease may be conveniently classified into 3 categories: (1) symptoms and signs due to inadequate circulation, (2) symptoms and signs due to collateral circulation, (3) associated symptoms and signs.

1. Symptoms and signs due to inadequate circulation (table 2).

(A.) Inadequate cerebral circulation.

Most of the patients complained of dizziness or vertigo at some stage of their illness.[3, 4] Our patient had objective vertigo that was progressive in nature. These symptoms were often precipitated or aggravated by physical exertion, which apparently increased the discrepancy between supply and demand. Syncope as a symptom was first described by Lewis and Stokes;[14] from information in the literature as well as clinical analysis of our case, it would appear that any of the following mechanisms might be responsible for the syncope associated with this disease: 1. Hyper-

TABLE 2.—*Symptoms and Signs Due to Inadequate Circulation*

Cerebral	Eye	Facial Anemia	Upper Extremities
Dizziness	Amaurosis fugax	Muscular atrophy	Rapid exhaustion
Vertigo	Black spots	Ulcerated palate	Claudication
Aphasia	Amblyopia	Perforated nasal septum	Absent pulsations
Syncopal attacks	Decreased visual acuity with activity	Claudication of muscles of mastication	Trophic changes in nails
Headache	Cataracts	Saddle nose deformity	Ischemic color changes
Transitory hemipareses or hemiplegias	Retinal atrophy	Thin pigmented skin	
Convulsions	Retinal pigmentation	Atrophy of alveolar processes	
Mental impairment	Photophobia	Ulcerated nose	
	Leucomata		
	Peripapillary arteriovenous anastomoses		
	Glaucoma		
	Optic atrophy		
	Sluggish blood flow in the retinal vessels		
	Atrophy of iris		

sensitive carotid sinus, (a) due to bradycardia, (b) due to hypotension, (c) due to cerebral ischemia; 2. cerebral ischemia; 3. orthostatic hypotension. In the literature the frequency of the hypersensitive carotid sinus syndrome in patients with pulseless disease has been emphasized, this association being noted in at least 7 cases.[3] The increased sensitivity has been thought to be due to scar tissue in the area of the sinus causing traction on movement of the head. It is difficult for us to understand how pressure over the carotid sinus with resultant syncope can be ascribed even partially to hypersensitivity in a patient in whom this pressure removes the sole source of cerebral circulation. In our patient, very minimal pressure over the left carotid sinus caused syncope; since this vessel was the only pulsatile one remaining in the neck, we assumed the syncope was due to cerebral ischemia per se rather than a hypersensitive carotid sinus. However, there is 1 case reported of hypersensitive carotid sinus occurring after ipsilateral ligation of the common carotid and internal carotid arteries that responded favorably to removal of the carotid bifurcation.[17]

(B.) Inadequate circulation to the eyes.

The ocular manifestations were emphasized in the Japanese literature by the ophthalmologists and have been considered by some as essential to the diagnosis[1, 12]; as might be anticipated, however, there are all degrees of ocular anemia. Our patient had no subjective or objective evidence of eye involvement.

Lewis and Stokes[14] have described the only instance of optic atrophy; the type of involvement most commonly emphasized has been the striking peripapillary anastomoses.[12] The interesting observation has been made that all of the ocular signs are exaggerated in the sitting or standing position;[3] further, the retinal pathology usually precedes the corneal pathology, and the right eye was involved earlier and more severely than the left eye.[3, 15, 18] In many cases the ocular complaints dominated the clinical picture.[12, 16]

(C.) Inadequate circulation to the face. Our patient demonstrated advanced facial atrophy with a bird-like facies, atrophic pigmentation, and a thinned skin. The adverse cosmetic effects are self evident.

(D.) Inadequate circulation to the upper extremities. Manifestations in the upper extremities have been surprisingly mild, apparently due to the gradual onset of the disease, the development of collateral circulation, and the probable utilization of preformed collateral channels.[5] Although trophic changes may be present in the upper extremities, only 2 patients have complained of claudication in the arms.

2. Symptoms and signs due to collateral circulation.

Palpable superficial arteries on the outer chest wall have been frequently noted.[14, 15] Crenations of the ribs have also been described and should be diligently sought for.[5] Machinery murmurs with systolic accentuations may be audible over the areas of the collateral vessels. No evidence of collateral circulation was found in our patient. The term reversed coarctation has been used for this syndrome because the collateral blood flows in a cephalad direction instead of a caudad direction, as in a true coarctation of the aorta.[7] In 1 patient the diagnosis of patent ductus arteriosus was suspected because of a continuous murmur, probably due to dilated and tortuous arterial collateral channels.[12, 13]

3. Associated symptoms and signs.

Changed auditory perception in this condition has been mentioned.[19, 20] Some patients have tachycardia at rest. Arterial hypertension in the lower extremities has been described[18] and many explanations have been offered for it. However, this finding has been observed in only a minority of cases and the opposite condition prevailed in our patient, namely, relative hypotension in the lower extremities. Cardiovascular manifestations have been reported, including 4 instances of angina pectoris.[5] The pathogenesis of the coronary artery disease may well be involvement of the coronary ostia with chronic inflammatory disease. The only laboratory findings of significance are an elevated erythrocyte sedimentation rate and a leukocytosis in the great majority of cases;[3-5] the absence of these findings in any given case may reflect the duration of the disease with the stage of active inflammation having passed.[5]

Pathology

Although different terms have been given to this entity, the anatomic descriptions are very similar.[3, 5, 6] The condition has been called thromboangiitis obliterans,[4] periarteritis nodosa,[21] periarteritis of the major arteries,[13] tuberculosis,[4] and syphilis.[8-11] The involved vessels show a panarteritis involving all the layers of the wall with a resultant obliteration of the lumen[3, 6]; in some cases attempts at recanalization have been noted.[3] Important is the absence of fibrinoid necrosis. The inflammatory infiltrate consists chiefly of lymphocytes and plasma cells with predominant involvement of the media and the vasa vasorum.[5, 6] There is usually a proliferation of the intima and a fibroblastic proliferation of the media with occasional, inconstant giant cells in the media; round cells may be present between the adventitia and the media.[3, 5] The giant cells may resemble those seen in tuberculosis; however, no organisms have been found even with the presence of acid-fast stains.

The pathologic process appears to be localized to the innominate, subclavian, and carotid arteries; however, the condition may extend to just below the base of the skull.[18] In the few postmortem examinations reported, the carotid artery and, by adventitial spread, the carotid sinus have usually been involved.[18] There has not been any involvement of the intracranial vessels. Depsite the universal involvement of the branches of the arch of the aorta and the absence of involvement of other vessels in the clinical material, there have been a few case reports of histologic involvement of visceral vessels.[18, 22] Harbitz[22] described an infiltrative lesion of the abdominal aorta with cartilaginous consistency; Frovig[18] described involvement of the superior mesenteric artery; involvement of the orifices of the coronary arteries and the pulmonary arteries has also been described.[3, 6] Ask-Upmark reported a patient with renal hypoplasia supposedly due to involvement of the renal artery.[3] As already mentioned, the entire thoracic aorta was involved in a case reported from the Mayo Clinic.[6] It must be emphasized that no case has been reported, to the authors' knowledge, with complete obliteration of the aortic lumen; this disease state primarily involves the branches of the aorta. The additional anatomic changes result from the collateral circulation, chiefly from the intercostal branches of the descending aorta communicating with the subclavian arteries. Crenation of the lower borders of the ribs,[14, 18] and prominent superficial arteries on the abdominal wall and dorsal thorax have been seen.[14, 15]

Etiology

Up to the present time the etiology of this condition has been obscure. Although pathologic findings have been reported occasionally consistent with well-known disease states, these have not been uniform or consistent in the material available.[3, 4] Furthermore, it must be recognized that most diseases, at one time or another, may have bizarre manifestations that overlap other well-defined disease states; examples of this overlapping are particularly common in the collagen vascular diseases and in the group of malignant lymphomas and leukemias. The presence of the bizarre atypical cases, however, should not detract from our attempt to categorize the typical case in an orderly way. We believe that such reasoning is particularly pertinent in this disease. Since the majority of the pathologic findings have indicated a nonspecific arteritis, the few case reports of apparent specific but atypical etiologies should not lead us astray. The various etiologies that have been mentioned will be considered individually.

Syphilis has been mentioned because of the predilection of the syphilitic aneurysms for the ascending arch of the aorta; however, none of the case reports accepted in this review had evidence of aneurysm. All 22 patients in whom serologic tests were determined had negative results. No evidence of syphilis has been found pathologically.

The pathologic lesion closely resembles that seen in tuberculosis, including the occasional mention of Langerhans' cells.[4] One patient in the Japanese series had evidence of active pulmonary tuberculosis;[4] however, the almost universal absence of tuberculosis elsewhere, the absence of tubercle formation and caseation necrosis, the peculiar anatomic localization, and the vascular involvement that is rarely encountered in tuberculosis are points that strongly militate against the diagnosis of tuberculosis.

The chief point of similarity between lupus erythematosus and thrombotic obliteration of the branches of the aortic arch is the predilection for young women. However, the peculiar anatomic localization, the absence of systemic symptoms or signs, the absence of leukopenia with a tendency toward leukocytosis, the absence of skin rashes, and the negative peripheral blood preparation for lupus erythematosus tend to eliminate this condition from consideration. The negative lupus erythematosus preparation in our patient is thought to be the first instance in which this diagnostic test was used in a patient with thrombotic obliteration of the branches of the aortic arch.

Periarteritis nodosa should be discarded as a possibility because of its tendency to affect men with pathologic involvement of smaller vessels and striking fibrinoid necrosis. There is no evidence in the literature of involvement of large-sized arteries in periarteritis nodosa. Furthermore, the absence of hypertension, cardiomegaly, fever, albuminuria, neuritis, and allergic manifestations in thrombotic obliteration of the branches of the aortic arch seems to eliminate periarteritis nodosa from consideration.

Cranial arteritis also has a peculiar localization, which, however, differs from the condition under question. Biopsies of affected vessels show a panarteritis with giant cells that closely simulates that found in thrombotic obliteration of the branches of the aortic arch. There have been reports of involvement of occipital, radial, facial, carotid, brachial, and cerebral arteries in temporal arteritis.[23] However, the latter condition usually involves the 55 to 80 age group, shows no preference for the female sex, and exhibits a different anatomic localization. Although a relationship between these conditions cannot be denied, it would appear wiser, for the present time, to consider them as separate entities.

It is pertinent to mention that necrotizing angiitis has been offered as a convenient generic term for the group of vascular diseases, including hypersensitivity angiitis, allergic granulomatosis, rheumatic arteritis, periarteritis nodosa, and cranial arteritis[23]; however, the pathologic *sina qua non* for the diagnosis of this group is fibrinoid necrosis plus a panarteritis; since the disease under discussion has in no case demonstrated fibrinoid necrosis, it would by definition be excluded from the category of necrotizing angiitis.

Thromboangiitis obliterans (Buerger's dis

ease) differs from thrombotic obliteration of the branches of the aortic arch by virtue of differences in age and sex predilection, different anatomic localization, and the commonly associated thrombophlebitis. However, the pathologic picture, the end result in the arteries, and the size of arteries attacked, are similar in these 2 conditions. Accordingly, the term thrombotic obliteration of the branches of the aortic arch was thought to be an appropriate designation, as it reflects the close relationship to Buerger's disease, while, at the same time, emphasizing the different anatomic localization.

In the reported cases of pulseless disease, there has been no instance of clinical involvement of the extremities; in the few postmortem examinations reported, there has been no mention of involvement of peripheral vessels. Thus, from a purely pathologic standpoint, we cannot completely eliminate Buerger's disease as a diagnostic possibility. The smoking habits of patients with pulseless disease have generally not been commented upon. Our patient smoked an average of 10 cigarettes per day.

The following conditions, which at first sight might appear to be related to the condition under question, cannot be incriminated because of obvious clinical and pathologic differences: Wegener's granulomatosis, sarcoidosis, the mycoses, brucellosis, giant-cell arteritis, leprosy, arteriosclerosis, and congenital malformations. To the authors' knowledge, there has been no case of congenital malformations that resulted in absence of pulses in both upper extremities. It should be re-emphasized that 1 or 2 cases may demonstrate some of the histologic characteristics of 1 of the above diseases, but the failure to demonstrate these characteristics consistently in all, or even in the majority, of the cases casts a great deal of doubt on the pathogenetic relationship.

Prognosis

Because of the paucity of clinical material, no clear-cut statement can be made concerning prognosis. The time that has elapsed in cases cited in the literature from the apparent onset of the condition to death varies from 1.5 years to 14 years; the usual cause of death is cerebral ischemia in some form. Obviously, accurate statistics on longevity are difficult to obtain, as it is difficult to date the onset in any individual case. One might conservatively conclude that this disease significantly reduces the life span of an affected individual.

Treatment

Because the etiology of this condition is unknown, it might be anticipated that there is no specific treatment. The following methods of treatment have been advised: change of climate, minimizing the recumbent position, exercise short of claudication, Buerger's exercises of the upper part of the body, antibiotic, anticoagulant, and vasodilator agents, steroid therapy, androgen therapy, cervical sympathectomy, and symptomatic treatment. The number of therapeutic procedures advocated indicate the lack of specificity of any given one. Certain general measures seem to be in order: All smoking should be eliminated, because of the close relationship to Buerger's disease; digitalis should be used cautiously because of its known ability to increase the sensitivity of the carotid sinus; prophylactic atropine therapy in patients with syncope should be administered cautiously, if at all, because of the danger of precipitating or aggravating glaucoma; long-term anticoagulant therapy appears to be rational because of the relation of the arterial occlusions to the symptoms. More definitive therapy may be forthcoming with recent surgical technics of endarterectomy, local resection, and homotransplantation.

Summary

The sixth case of so-called "pulseless disease" to be recorded in the American literature has been presented. The use of the more descriptive term "thrombotic obliteration of the branches of the aortic arch" has been suggested. The world's literature has been reviewed and the clinical material presented. Therapeutic recommendations and admonitions have been made

Addendum

Subsequent to the preparation of this paper, an additional case of this condition has been reported

from the United States. (Thrombotic Occlusion of the Branches of the Aortic Arch, Martorell's Syndrome. Report of a case treated surgically. Davis, J. B., Grove, J., and Julian, O. C. Ann. Surg. **144:** 124, July 1956.) The patient was a 51-year-old white man who had a surgical removal of a clot from his innominate artery with alleviation of his cerebral symptoms.

Summario in Interlingua

Es presentate un caso del si-appellate "morbo sin pulso." Illo es le sexte caso publicate in le litteratura american. Es proponite le uso del plus descriptive termino "obliteration thrombotic del brancas del arco aortic." Es passate in revista le litteratura mundial in re iste thema. Datos clinic es presentate. Recommendationes e admonitiones therapeutic es sublineate.

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What is spoken of as a "clinical picture" is not just a photograph of a man sick in bed; it is an impressionistic painting of the patient surrounded by his home, his work, his relations, his friends, his joys, sorrows, hopes, and fears.—Francis Weld Peabody. *The Care of the Patient.* Harvard University Press, 1927.

Measurement of Cardiac Output and Central Volume by a Modified Decholin Test of Circulation Time

By HADLEY L. CONN, JR., M.D., DONALD F. HEIMAN, M.D., AND CLAUDE R. JOYNER, M.D.

A technic is described for determining mean circulation time, cardiac output, and central blood volume by use of graded dosages of sodium dehydrocholate (Decholin) administered into a peripheral vein. The indicator-dilution curves derived by the technic were compared with radiopotassium-dilution curves obtained simultaneously in 12 patients. The results showed a surprisingly good agreement between the 2 methods and indicate that the traditional Decholin test of circulation time can be modified to provide much more information than it has in the past.

THE determination of arm-to-tongue circulation times by the sodium dehydrocholate (Decholin) method has a long history of clinical use. Still it has provided only limited quantitative or diagnostic information about the circulation and, for this reason, has been supplanted to a considerable extent by more complex methods. However, during the course of simultaneous radiopotassium-dilution curve and angiocardiographic studies in patients with rheumatic heart disease, we employed the times of appearance and disappearance of the Decholin taste to decide the timing of film exposures. It soon became apparent that we could frequently differentiate between mitral stenosis and insufficiency as well from the "Decholin" times as we could from the subsequently obtained dilution curves or Diodrast opacification patterns. This finding led us to appreciate that the Decholin test is fundamentally an application of the indicator-dilution principle in which Decholin serves as an indicator providing 2 subjective end points, the times of appearance and disappearance of the characteristic bitter taste. Therefore, we considered that these end points might be related to determinable, relatively constant blood concentrations of Decholin; if so, we might obtain multiple onset and offset times from multiple injections of graded doses of Decholin. These various times might then be appropriately related to the proper concentration coordinates so as to give adequate data for complete construction of an indicator-dilution curve. Such a curve would of course provide the same quantitative information on cardiac output and central blood volume as are provided by conventional dye and isotope-dilution technics.

These concepts were tested experimentally by (1) determination indirectly of the blood concentrations of Decholin associated with the appearance and disappearance of the bitter taste, (2) determination of these times of onset and offset of taste following injections of 3 graded doses of Decholin, (3) construction of Decholin-dilution curves from the data on circulation times and blood concentrations at taste threshold, and finally (4) comparison of the results obtained from these curves with results obtained from radiopotassium-dilution studies carried out simultaneously. Comparisons of curve contour, cardiac output, central blood volume, and mean circulation time were made in 12 patients with and without cardiovascular disease. The correlation between the isotope and Decholin results was surprisingly good and indicates that the Decholin method is capable of providing more information than has been obtained in the past.

METHOD

Twelve patients were studied—6 with rheumatic mitral valvular heart disease, 1 with aortic aneurysm, 1 with pulmonary hypertension, 2 with arteriosclerotic heart disease, and 2 with no known cardiovascular disease.

Each patient was given a preliminary injection

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This research was supported by grants-in-aid from the American Heart Association, the Atomic Energy Commission, and the Lycoming (Pa.) County Heart Association.

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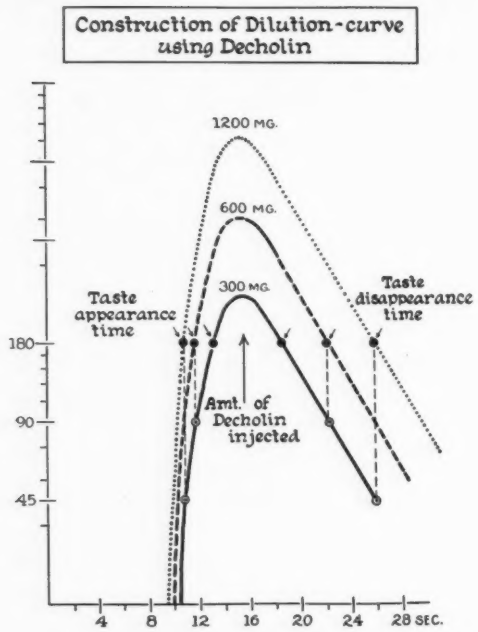

FIG. 1. Concentration of Decholin in mg./L. of blood plotted logarithmically (ordinate). Abscissa, time in seconds. The theoretical dilution curves would be obtained by injection of 300 mg., 600 mg., and 1200 mg. of Decholin. They are similar in contour and slope but differ in area in proportion to the size of the Decholin dose. The 3 pairs of appearance and disappearance times of bitter taste, determined by injection of graded doses of Decholin (solid circles), are plotted at a level corresponding to the mean threshold concentration required for appreciation of Decholin taste. The dotted circles designate points on a common curve derived by extrapolation of appearance and disappearance times.

of Decholin, usually 300 mg., so that he could learn to recognize the Decholin taste and subsequently to better determine its onset and offset times. This material was injected in a total volume of 30 to 40 ml. of physiologic saline into an antecubital vein through either a Robb-Steinberg cannula or a no. 15 hypodermic needle. All injections were made as rapidly as possible, 1 to 2 sec. usually being required. Following the trial injection, each patient was given in varying order, 300 mg., 600 mg., and 1200 mg. injections of Decholin. Onset and offset times of Decholin taste were determined to the nearest .25 sec. for each injection. The results were plotted, as described under the section on theory, in order to form dilution curves. Terminal slope value, cardiac output, mean circulation time, and central blood volume were calculated. Simultaneously with 1 and sometimes with 2, of the Decholin injections a radiopotassium (K^{42})-dilution curve was obtained by the addition of about 30 mc. of this indicator to the material injected. This technic has been described elsewhere.[2, 7] Slope value, cardiac output, mean circulation time, and central blood volume were likewise calculated from the K^{42} dilution curves.

With both technics, cardiac output was determined by the Hamilton-Stewart formula and central blood volume by the product of mean circulation time times cardiac output.

Theory and Method of Decholin Dilution Curve Construction. It was first assumed that Decholin can serve as an appropriate indicator for indicator-dilution studies—that is, that it mixes completely somewhere in the central circulation, that no significant amount is lost in the first circulation, etc. as discussed by Newman[3] and by Meier.[4] These assumptions, of course, were to be tested indirectly by the comparison of Decholin and K^{42} results. Then, assuming that Decholin fulfills these requirements, if onset and offset of the subjective taste occur at known constant blood concentrations of Decholin, these 2 concentration-time coordinates establish 2 points on a dilution curve. The constant relationship of blood concentration to taste was experimentally established as described in the results. Then, assuming constant cardiac output and central volumes, a second injection of a larger dose of Decholin will give a second curve of exactly the same (parallel) contour as that with the smaller dose, but one with relatively higher concentration levels at every point on the curve in proportion to the size of the 2 doses. Thus, the onset and offset times of taste will be at lower points on the second curve contour as compared to initial values as plotted on the first curve because of the unchanged concentration of Decholin required for threshold of taste. These second points can be extrapolated so as to become points on the first (or a common) curve by the process of placing the second points at the time intercepts experimentally determined, but at concentration intercepts reduced in proportion from the taste concentration threshold as the size of the second Decholin dose is related to the first. Additional points can be added to a common curve in the same fashion by using a third, still larger dose of Decholin. Theoretically, if enough injections of Decholin of different dosages were given, an infinite number of points reducible to a common curve could be obtained. Practically, the number of points obtainable is limited by the amount of Decholin that can safely be given to patients and by the precision of the end points of the test.

By the use of this technic, 6 experimental values (3 pairs of onset-offset times) were determined in all patients and plotted as described above. With experience we learned that the onset to peak circulation time interval of an indicator-dilution curve is 5 to 6 sec. in normal subjects, 6 to 8 with slight to moderate circulation time abnormalities, and 10 to 12 with

TABLE 1.—*Results Calculated from Decholin (D) and K^{42} Dilution Curves*

Case	Diagnosis	Slope (%/sec.)			Cardiac output (L./min.)			Mean circulation time (sec.)			Central volume (liters)		
		D	K^{42}	D/K^{42}	D	K^{42}	D/K^{42}	D	K^{42}	D/K^{42}	D	K^{42}	D/K^{42}
1	MS	23	22	1.05	9.5	10.7	0.89	18	17	1.06	2.9	3.0	0.97
2	MI	1.7	2.3	0.74	1.7	2.4	0.71	70	66	1.06	2.0	2.4	0.83
3	PH	23	24	0.96	10.1	10.2	0.99	17	16	1.06	2.9	2.7	1.07
4	N	17	15	1.13	6.8	8.0	0.85	19	18	1.06	2.2	2.4	0.92
5	N	28	23	1.22	10.5	9.1	1.15	15	19	0.79	2.6	2.9	0.90
6	ASHD	20	21	0.95	6.0	7.8	0.77	17	17	1.00	1.7	2.2	0.77
7	DM ASHD	28	26	1.08	9.0	7.5	1.20	15	14	1.07	2.3	1.8	1.28
8	AAA	17	14	1.21	5.8	5.9	0.98	21	25	0.84	2.0	2.5	0.80
9	MS	18	18	1.00	7.1	7.5	0.95	19	19	1.00	2.2	2.4	0.92
10	MI	6.0	7.0	0.86	4.0	5.0	0.80	33	30	1.10	2.2	2.5	0.88
11	MS	28	23	1.22	8.4	8.5	0.99	16	18	0.89	2.3	2.5	0.92
12	MS	12	12	1.00	6.0	6.7	0.99	20	18	1.11	2.0	2.0	1.00
		Mean		1.03	Mean		0.93	Mean		1.00	Mean		0.94

N = normal; MS = mitral stenosis; MI = mitral insufficiency; PH = pulmonary hypertension; ASHD = arteriosclerotic heart disease; DM = diabetes mellitus; AAA = abdominal aortic aneurysm.

moderate to marked prolongations of circulation times. Thus an additional "approximate" point was added by use of these time intervals, via the process of tracing upward the slopes of the apparent ascending and descending limbs of the curve until they intersected at the appropriate time intercept. The descending limb was constructed as the exponential slope best fitting the offset time plots and the ascending limb as the best natural curve through the onset time plots, all plotted on a semi-log scale. In this fashion the complete Decholin-dilution-curve contour was established. This construction is illustrated in figure 1.

RESULTS

It was quickly appreciated that both the onset and offset of taste were consistently recorded (within ±1 sec. and usually +1) at identical levels of K^{42} concentration as recorded from the curves obtained from simultaneous radiopotassium injections. Thus it seemed apparent that onset and offset of taste were likewise occurring at approximately the same Decholin blood concentration levels. Second, it appeared from the curves that these "taste" times were noted at about the same concentration level in each patient. By comparing the blood concentration of K^{42} in relation to the amount given (at the times of appearance and disappearance of taste), with the expected Decholin concentration in relation to the amount of Decholin given, an average concentration of 180 mg./L. was calculated as the threshold level required for appreciation of the Decholin taste. This varied only from 170 to 205 mg./L. in 10 of the 12 patients but was calculated to be 140 mg./L. in 1 and 250 mg./L. in another.

The mean value was subsequently employed for calculating cardiac output central volume from all curves. That is, 180 mg./L. was used as a constant concentration value on the abscissa of the scale at which all times of appearance and disappearance of taste were initially plotted preparatory to construction of a common curve.

The calculated results are shown in table 1. The ascending limbs of the K^{42} and the Decholin curves agreed exceptionally well in all instances although no quantitative analysis of the degree of agreement was attempted. The K^{42} and the exponential values of the Decholin terminal slope agreed in every instance within 26 per cent. The mean difference was only 3 per cent (using K^{42} results as reference standard) so that the mean ratio Decholin slope/K^{42} slope was 1.03. The cardiac output values agreed within ±29 per cent in each instance and the mean difference was only 7 per cent so that the mean ratio of Decholin cardiac output/K^{42} cardiac output was 0.93. If the data on cardiac output

from patients 2 and 10 are excluded on the grounds that the curves had terminal slopes so flat that recirculating indicator amounts were included in the Decholin curve reconstruction and therefore made calculated output too low to that extent, the ratio increases to 0.98 and the greatest variation between the 2 methods is reduced to 23 per cent. Mean circulation times (*MCT*) by the 2 methods agreed in each instance within ±21 per cent. The mean difference was 0, the mean ratio of Decholin $MCT/K^{42}/MCT$ being 1.00. Central volume (*CV*) determinations agreed in each instance within ±28 per cent. The mean difference here was 6 per cent and the mean ratio of Decholin $CV/K^{42}/CV$ was 0.94.

No further formal statistical analysis was attempted because it is probably erroneous to consider this group as a homogeneous one. For example, the errors noted above due to recirculation are presumably minimal in patients with large flows and small volumes, but apparently appreciable with the reverse. Approximately, however, the standard deviation between the 2 methods with regard to all the calculated parameters appears to be of the order of ±15 per cent under conditions in which blood flow and volume derangements were not abnormal in the extreme. It also appears that this random variability is of sufficiently great magnitude to make impossible any demonstration as to whether the differences in individual or mean ratios are indicative of systematic variation (error). It seems logical, however, to anticipate systematic underestimation of blood flow in patients with exceptionally prolonged taste times, since these times must mirror the added concentration of recirculating Decholin, however great it may be.

Discussion

The results indicate that a surprisingly accurate indicator-dilution curve can be constructed, at least in many patients, from recordings of the times of appearance and disappearance of the bitter taste following antecubital injections of 3 graded dosages of Decholin. Consequently, surprisingly accurate results for cardiac output, mean circulation time, and central volume are also obtained from these curves with the general limitations of any indicator-dilution method and the specific limitations imposed by the technic employed. The pulmonary mixing volume[3] and the amount of valvular regurgitant blood flow[4] can also be calculated subject to the same restrictions and the validity of those methods. With the K^{42} method taken as a fixed standard (i.e., one with no random or systematic error), it appears that the Decholin technic gives results for circulation time, blood flow, and central blood volume with a random variability of the order of 15–20 per cent (S.D.) and no demonstrated systematic error in a patient group such as ours. Since the K^{42} method obviously has some variability itself, the true standard deviation is presumably even somewhat less. With more extensive testing it seems likely that a significant systematic underestimation of flow can be demonstrated under conditions of severely prolonged circulation times.

The following matters are those that we believe provide the major sources of error. The hemodynamic state of the subject and the speed of Decholin injection, must be essentially constant in order that the 3 determinations can be correlated properly. Second, the test has subjective end points and the patients sometimes do not appreciate the disappearance of the Decholin taste as well as its appearance. Therefore, considerable care must be exerted in making as certain as possible that the recorded "disappearance" times are valid. Even so, gross discrepancies sometimes occur, which in our studies could be resolved only by drawing the best fit through the experimental points. Third, when mixing volumes are large and blood flow is slow, the concentration critical for taste may not be reached, especially with the smallest doses. Under these circumstances injections containing larger amounts are required to obtain the usual number of points. These amounts may be undesirably large. Fourth, since the greatest accuracy in curve construction can be obtained, in most instances, by treating the terminal portion of the slope as a decreasing exponential, unduly flattened slopes may be obtained in patients with prolonged circulation times. This occurs simply because it is impossible to correct properly for recirculating material. In these patients even

though the proper appearance-disappearance times are recorded, the true primary dilution curve may be difficult or impossible to reconstruct. Here the main effect will be a systematic error with calculated output too low and mean circulation times too long. Either more injections of appropriate Decholin dosages or a correction factor is required to improve accuracy. Fifth, limitations are imposed by the time and variations in time required for Decholin in the blood to diffuse sufficiently to activate the taste receptors, for the neuronal circuits to respond, and for the patient to signal appearance and disappearance of taste. The close resemblance of the K^{42} and Decholin curves suggests, however, that these events do not introduce appreciable error and therefore must all proceed with considerable speed and consistency in most subjects. Sixth, the elevated cardiac output found in several patients suggests that rapid injections of 40 ml. of fluid cause a mild cardiac stress. Thus, if information on the circulatory state under more basal conditions is desired, injections of smaller total volume seem indicated.

In spite of our present inability to evaluate completely and quantitatively the importance of these limitations, the good correlation of the Decholin and K^{42} results indicates that the net effect does not commonly prevent a valid assessment of the existing dilution-curve slope value, cardiac output, mean circulation time, and central volume. As measurements of these parameters have not, to our knowledge, been attempted from analysis of arm-to-tongue circulation times, this accuracy in quantitation indicates that the Decholin test can be made to yield much more information than it has heretofore.

The obvious advantages of the test are that it can be accomplished without special preparations, recourse to unusual devices or materials, or any appreciable danger to the patient, and furthermore it can be accomplished in a short period of time at the bedside. The test can therefore be done on almost any patient by any member of a ward staff following minimal instruction of each. Whether the accuracy obtainable under "ward" conditions will be sufficiently great, and whether the information gained in proportion to the time required in calculations will prove sufficiently valuable to warrant replacement of the traditional single injection arm-to-tongue Decholin circulation time with the more informative multiple, graded-dose technic remains to be determined.

Summary

A method for constructing an indicator-dilution curve from multiple, graded-dosage Decholin circulation times is presented.

This method was applied in 12 patients for measurement of mean circulation time, cardiac output, and central volume. The results obtained were compared with those obtained from simultaneously recorded radiopotassium-dilution curves.

In all patients every comparison agreed within ±30 per cent. The mean ratios of mean circulation time (Decholin)/mean circulation time (K^{42}), cardiac output (Decholin)/cardiac output (K^{42}), and central volume (Decholin)/central volume (K^{42}) were 1.00, 0.93, and 0.94, respectively. The blood concentration of Decholin associated with appearance and disappearance of the characteristic bitter taste averaged about 180 mg./L.

The results show that at least under several varying conditions a modified measurement of Decholin circulation time can be used to give more quantitative information than it has traditionally been used to provide.

Summario in Interlingua

Es presentate un methodo pro le construction de un curva de dilution del indicator ab multiple tempores circulatori a Decholina in doses graduate.

Iste methodo esseva usate in 12 patientes pro le mesuration del tempore circulatori medie, del rendimento cardiac, e del volumine central. Le resultatos obtenite esseva comparate con le resultatos obtenite per simultanee registrationes de curvas de dilution de kalium radioactive.

In omne le patientes omne le comparationes esseva de accordo intra un margine de ±30 pro cento. Le proportion medie de tempore circulatori medie per Decholina a tempore circulatori

medie per K^{42} esseva 1,00; illo de rendimento cardiac per Decholina a rendimento cardiac per K^{42} esseva 0,93; e illo de volumine central per Decholina a volumine central per K^{42} esseva 0,94. Le concentration de Decholina in le sanguine, associate con le apparition e disparition del characteristic gusto amar habeva un nivello medie de 180 mg per L.

Le resultatos prova que un modificate mesuration de tempores circulatori a Decholina pote esser usate, al minus sub certe conditiones de varie generes, pro obtener plus extense informationes quantitative que lo que ha traditionalmente essite obtenite per medio de illo.

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Nine patients, 6 with disseminated lupus erythematosus and 3 with periarteritis nodosa, have been treated with metacortandracin. One patient with periarteritis nodosa died while under treatment. The autopsy showed extensive arterial involvement, both visceral and peripheral. The most remarkable feature in the histologic study was the lack of inflammatory process noted in the diseased arteries. The inference from these studies is that, if this patient had been treated in the early phase of the disease, the outcome would have been more favorable. The other 2 cases of periarteritis nodosa have been converted from very ill people to a status of employability. All 6 patients with disseminated lupus erythematosus had previously been treated with either cortisone or corticotropin. All have done much better with metacortandracin. However, in no instance have the L.E. cells disappeared from the bone marrow or from the peripheral blood. All 6 cases carry on their usual activities with little or no restriction. The capacity to tolerate a normal diet, without salt restriction or the addition of the large, gastric-disturbing doses of potassium required with the use of other steroids, is appreciated by these people. The initial dose was 10 mg. every 8 hours in all cases except 1. The dose was decreased by 5 mg. every 5 days until the smallest amount required for maintenance was reached. It was usually 15 to 20 mg./day. All these patients with 1 exception have been observed under treatment for 60 to 120 days. Although the short-term treatment has been favorable, more time will have to elapse before a conclusive opinion can be reached as to long-term treatment of the collagen diseases with this new compound.

Wendkos

Effect of Cigarette Smoking on Coronary Blood Flow and Myocardial Metabolism

By L. M. Bargeron, Jr., M.D., D. Ehmke, M.D., F. Gonlubol, M.D., A. Castellanos, M.D., A. Siegel, M.S., and R. J. Bing, M.D.

The effect of smoking on the heart has been a controversial subject. The present studies were undertaken to investigate the effect of cigarette smoking on the coronary flow, myocardial usage of oxygen and myocardial extraction of glucose, pyruvate, lactate, and ketones. Catheterization of the coronary sinus revealed that cigarette smoking in patients without heart disease results in a significant rise in coronary blood flow and heart rate and a significant decline in coronary vascular resistance and myocardial extraction of oxygen and glucose. No evidence of coronary vascular constriction was detected.

THE most important pharmacologically active constituent of tobacco smoke is nicotine. From 1 to 4 mg. of this alkaloid are absorbed from each cigarette into the blood stream during smoking.[1, 2] The primary action of nicotine consists of a transient stimulation followed by depression of all sympathetic and parasympathetic ganglia.[3] Nicotine has a similar effect on skeletal muscle and the central nervous system, and may act directly on smooth muscle. It probably causes vasoconstriction in blood vessels and, in the intestine, increased motility.[4] Action of nicotine on the central nervous system first results in stimulation of the respiratory, vasomotor, and emetic centers.[5] Burn and associates[6] have shown that nicotine exerts its antidiuretic action through stimulation of the supraoptic hypophysial system with a resultant release of posterior pituitary hormone. The release of epinephrine is also said to occur with small doses of nicotine.[7]

Despite these generally accepted actions on specific tissue, the effect of smoking on the heart has been a controversial subject. The experimental literature on the effect of nicotine on animal and heart-lung preparations is contradictory. In 1912 Meyer,[8] using large doses of this alkaloid (10 mg.), showed in experiments on dogs that nicotine had a constrictive effect on the coronary vessels. Morawitz and Zahn[9] found almost identical results in cats, using 5 mg. of nicotine. This was confirmed by Romm and Kuschnir[10] on rabbits. In contrast, Mansfeld and Hecht,[11] using the heart-lung preparation, found that the coronary blood flow increased 7 times when nicotine or tobacco smoke was added to the preparation. This was true whether enervated or denervated preparations were used. Deitrich and Schimert[12] gave nicotine to 19 dogs in doses of .01 mg. to 25 mg. They found increased coronary blood flow in all of their animals. Bellet and associates[13] showed in experiments in dogs with ligated coronary arteries that the amount of nicotine required to elicit electrocardiographic changes was only one fourth of the amount required to produce minimal changes in normal animals. Recently, Stein and Weinstein[14] have shown that ergonovine produces ballistocardiographic changes in subjects with atherosclerosis and arteriosclerosis, but not in normal subjects. Rinzler and associates[15] discovered that in atherosclerotic rabbits ergonovine or nicotine produced progressive electrocardiographic changes. He has also subsequently measured coronary flow in the perfused hearts of both normal and atherosclerotic rabbits. Nicotine produced an increased blood flow through the coronary vessels of the normal heart and a marked decrease in flow in the atherosclerotic heart. Recently, Schmitthenner and co-workers[16] measured the coronary circulation in the dog following intravenous injection of nicotine. He found with the nitrous oxide method that the

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Supported by the U. S. P. H. S. Grant H-1129(C4), the Life Insurance Medical Research Fund, the American Heart Association, and the Tobacco Industry Research Committee.

coronary flow and myocardial oxygen uptake increased, coronary resistance fell, and blood pressure rose. It appears from this review of the literature that, in general, small quantities of nicotine increase the coronary flow in dogs and rabbits, while large doses cause vasoconstriction.

The development of the electrocardiogram and ballistocardiogram has made it possible to estimate the effect of smoking on normal and atherosclerotic human subjects. Electrocardiographic changes during smoking consist of an increase in heart rate, a slight depression of the ST segment, and flattening of the T waves. Von Ahn[17] has shown in extensive studies of normal individuals that all of these changes were secondary to increased heart rate. He concluded that the electrocardiographic changes produced by smoking or by nicotine in persons with clinically healthy hearts were probably not of coronary origin. Recently, a large series of studies has been published using the ballistocardiograph to measure the effects of smoking on the heart. Henderson,[18] using the high-frequency bed ballistocardiograph, found no significant changes in 50 healthy young persons. In 30 subjects from 40 to 60 years of age, temporary alterations occurred after smoking. In 40 subjects with coronary disease, the ballistocardiogram showed abnormalities in 38 per cent after smoking. This experience has been confirmed by Kelly and Simon and their coworkers.[19, 20] Russek and others[21] found deterioration in the electrocardiograms on 18 of 37 subjects with coronary artery disease. Davis and his group[22] have reported the effect of smoking on 250 normal subjects and 190 patients with coronary disease. They found that smoking resulted in ballistocardiographic changes in 7.5 per cent of the control subjects and 48.9 per cent of the coronary group. No real change occurred in control subjects under the age of 40, and only 3 of 89 in the fifth decade showed alterations. Ballistocardiographic deteriorations occurred immediately after smoking in most patients.[22] There is no suggestion in these studies to support the concept that smoking causes coronary vasoconstriction in the normal man.

Direct studies on the effect of cigarette smoking on coronary blood flow of man have not been performed. It was the purpose of this investigation to measure the changes caused by cigarette smoking on coronary blood flow, coronary vascular resistance, cardiac output, heart rate, and myocardial extraction of lactate, glucose, pyruvate, and ketones.

Methods

The tests were attempted on 30 adult volunteers, both male and female, smokers and nonsmokers, who were kept in a fasting state for 12 hours prior to the procedure. Prior to the test, the subjects were fully informed of the nature of the procedure and their written consent was obtained. Coronary sinus catheterization was successfully performed on 14 of them. Their ages ranged from 18 to 53 years. None of the volunteers was known to have coronary disease. A cardiac catheter was inserted into the right atrium and a needle into the right femoral artery. Cardiac output was determined by the Fick principle. With the patient in the left lateral position the catheter was inserted into the coronary sinus. Simultaneous arterial and coronary sinus blood samples were drawn for glucose, ketones, pyruvate, and lactate determinations. The coronary blood flow was determined by the nitrous oxide method.[23] After the samples for the determination of the coronary blood flow were obtained during the control period, nitrous oxide was continued for an additional 10 minutes. At the end of a total of 14 minutes of nitrous oxide inhalation, the nitrous oxide was discontinued and the patient smoked a cigarette while the coronary blood flow was again measured by means of the nitrous oxide desaturation method.[24] Previous work from this laboratory has indicated that the saturation method and the desaturation method with nitrous oxide give identical results. Arterial and coronary sinus samples were again drawn and the cardiac output was measured. Myocardial usage of foodstuffs and of oxygen per 100 Gm. of heart muscle was calculated as the product of the coronary flow per 100 Gm. of heart muscle times their respective myocardial extractions.

The only untoward reaction noted during the procedure was a precipitous drop in blood pressure to shock levels, which occurred in 5 subjects immediately after or during smoking, and which was accompanied by pallor, nausea, and sweating. As soon as the fall in blood pressure was noted, the procedure was discontinued. The patients recovered in from 2 to 5 minutes with a rapid return to normal blood pressure. In 3 of these 5, the coronary blood flow had already been determined during smoking. It seems likely that these episodes were due to nicotine rather than the technical procedures carried out, since none of these symptoms has ever been observed during

TABLE 1—*Hemodynamic Data*

Name, age, date	Wt. (lb.) Ht. (in.)	S.A.	Cardiac output (ml./min.)	Cardiac index (L./M.²/min.)	Heart rate (beats/min.)	Mean B.P. (mm./Hg)	O_2 consumed (ml./min.)	Peripheral Resistance	L. V. wt. (Gm.)	Coronary O_2 extraction (vol. %)	Systemic O_2 extraction (vol. %)	Coronary Resistance (mm. Hg/100 Gm./min.)	Coronary flow (μ/min./100 Gm.)	O_2 usage (L.V./ml./min.)	Energy cost (Kg.M.)	L.V. work (Kg. M.)	Efficiency (%)
O.M., 29, B*	119	1.57	3440	2.19	90	83	231	37.9	114	10.58	6.7	.772	101	12.10	25.4	3.75	14.8
10/13/55, A†	65½	1.57	5490	3.49	89	80	201	22.9	114	7.90	5.1	.552	137	14.10	18.1	3.23	17.8
W.F., 24, B	—	—	6340	3.66	96	95	366	25.9	141	13.91	5.74	1.50	60	11.70	24.7	8.90	35.9
11/22/55, A	—	—	—	—	120	71	—		141	—	—	.660	110	—	—	—	—
R.B.P., 40, B	145	1.73	—	—	85	102	—		151	12.07	2.10	1.515	64	—	24.4	—	—
11/30/55, A	66	—	—	—	96	81	—		151	—	—	.902	84	—	—	—	—
R.W., 25, B	144	1.83	9100	4.94	91	97	271	19.6	156	11.70	2.98	1.56	59	10.75	22.6	11.30	50.0
12/7/55, A	68½	—	4400	2.40	97	100	176	41.7	156	—	5.60	1.53	62	10.15	21.3	5.98	27.0
N.L., 20, B	127	1.60	7520	4.71	96	83	281	17.6	119	12.22	3.83	1.165	78	11.30	23.7	8.50	35.7
1/3/56, A	64½	—	4550	2.84	98	83	228	29.2	119	10.75	5.01	1.065	87	11.30	23	5.02	21.8
L.W., 39, B	185	2.0	6350	3.97	100	88	365	22.1	117	13.25	3.90	.896	106	7.60	15.8	7.00	—
1/9/56, A	70	—	—	—	98	88	273		117	13.25	—	.922	90	—	—	—	—
F.B., 43, B	130	1.66	6600	3.97	88	110	254	27.8	123	13.50	3.85	1.25	84	11.35	29.3	9.90	33.0
1/25/56, A	57	—	5200	3.13	96	110	284	35.2	123	12.40	5.80	1.35	78	11.60	24.4	7.78	24.6
C.P., 51, B	121	1.60	6250	3.90	90	70	260	17.9	114	11.88	4.16	1.38	47	6.36	13.3	5.95	44.8
1/26/56, A	66½	—	—	—	100	70	—		114	9.34	4.05	1.10	59	6.30	13.2	—	—
G.P., 41, B	178	—	5140	2.54	74	93	298	36.6	182	14.67	5.80	1.49	59	15.75	33.00	6.50	19.6
2/7/56, A	72½	—	4200	2.80	74	93	294	33.2	182	13.20	7.00	1.26	70	16.80	35.30	4.52	12.8
K.H., 18, B	101	1.4	3430	2.45	62	74	199	30.2	95.4	10.36	5.80	1.56	44	4.35	9.14	2.05	22.5
2/16/56, A	60½	—	—	—	64	72	—		—	—	—	1.15	58	—	—	—	—
M.O., 53, B	139	1.82	—	—	—	70	—	—	—	8.25	—	.98	67	5.50	16.7	—	—
3/12/56, A	72	—	—	—	—	—	—	—	—	—	6.60	—	76	—	—	—	—
O.S., 55, B	202	2.18	7620	3.48	—	78	—	23.5	—	—	—	—	—	—	—	—	—
3/28/56, A	75	—	8200	3.76	—	80	—	21.2	—	—	—	—	—	—	—	—	—
Number of paired observations				6	10	11		6		6		10	11	6		5	5
Range of change				1.30--2.54	24--2	3--24		22.1--15.0		0--2.68		.100--.840	50--16	2.00--.06		-.52--5.32	3.0--23.0
Mean change				-.568	+6	-4.09		+3.4		-1.543		-.260	+12.91	+.44		-2.684	-9.82
t				.96	2.43	1.47		.64		3.83		2.80	2.36	1.15		-3.32	2.29
p				>.30	<.05	>.10		>.50		<.02		<.05	<.05	>.30		<.05	>.05

* Before smoking.
† After smoking.

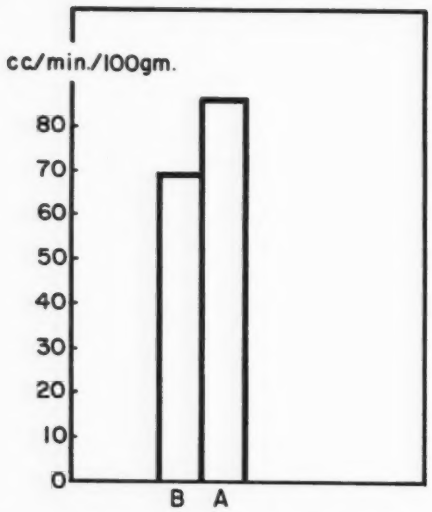

FIG. 1. Effect of cigarette smoking on the average values of the coronary blood flow in 11 subjects. Smoking resulted in a significant increase in coronary blood flow. *B* and *A* represent the average values obtained before and during cigarette smoking, respectively.

the measurement of coronary blood flow alone. Contributing to these episodes may have been the fact that the patients were asked to smoke at 20-second intervals rather than at their own leisure.

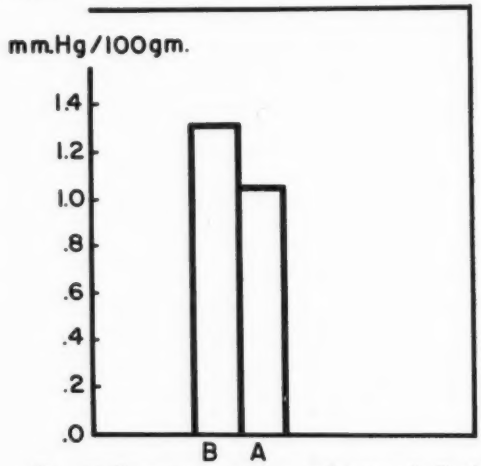

FIG. 2. Coronary vascular resistance declined significantly during cigarette smoking. *B* and *A* represent the average values obtained before and during smoking.

TABLE 2—*Metabolic Data, Blood Level and Myocardial Extraction*

Name	Glucose mg. %		Pyruvate mg. %		Lactate mg. %		Ketones mg. %	
	arter.	Δ	arter.	Δ	arter.	Δ	arter.	Δ
O.M., B*	96.1	2.4	.462	.164	7.10	1.920	4.23	1.440
666, A†	96.4	4.6	.372	.108	4.77	.070	4.11	1.320
R.B.P., B	107.6	3.0	.760	.138	12.83	.890	6.01	1.490
11/30/55, A	106.4	0.0	.622	.0	12.68	.0	6.28	2.200
R.W., B	109.8	0.5	.433	.034	5.84	.530	3.11	.660
12/7/55, A	108.2	1.8	.476	.034	6.81	1.770	3.78	.730
N.C., B	95.8	2.1	.578	.195	5.629	1.649	3.386	1.040
1/3/56, A	94.6	0.5	.552	.232	4.880	1.342	4.320	1.200
L.W., B	110.1	6.1	.494	.158	6.38	1.990	5.15	2.110
1/9/56, A	105.7	2.2	.477	.141	6.09	1.700	5.48	2.820
F.B., B	88.0	0.5	.449	.103	6.805	1.525	5.65	1.820
1/23/56, A	86.6	−0.9	.449	.103	6.560	1.650	7.04	3.000
C.P., B	89.7	1.4	.456	.176	3.039	0.848	3.54	−0.020
1/26/56, A	88.3	0.3	.403	.105	3.846	1.846	3.47	−0.020
G.P., B	89.0	10.8	.298	.084	6.020	2.626	1.370	0.152
2/7/56, A	94.0	8.3	.263	.052	4.810	1.375	1.561	0.419
H.W., B	90.35	2.35	.473	.122	7.34	2.660	4.65	1.480
12/1/55, A	88.25	0.35	.429	.087	6.28	2.230	4.31	1.030
S.W., B	97.3	7.1	.487	.139	9.65	3.500	1.219	.273
1/11/56, A	96.0	3.8	.469	.121	9.53	3.910	1.309	.407
Range	+2.2−−3.9		+.037−−.138		+1.24−−1.85		+1.18−−.450	
Mean	−1.53		−.033		−.2245		+.2661	
t	2.48		2.20		.74		1.77	
p	<.05		>.05		>.40		>.10	

* Before smoking
† After smoking

These untoward reactions occurred in both smokers and nonsmokers. Changes in the coronary circulation in patients who experienced syncopal attacks were similar to those whose blood pressure had remained unchanged.

Glucose was determined by the method of Hagedorn and Jensen, lactate by the method of Barker and Summerson, and pyruvate by the procedure of Friedemann and Haugen.[25-28] Ketones were analyzed with the method of Greenberg and Lester, as modified by Engel.[29]

Results

Table 1 and figure 1 show that coronary blood flow in 11 patients rose from a mean of 69.8 mm. per min. per 100 Gm. to 82.8 ml. per min. per 100 Gm. of heart muscle. This rise was statistically significant ($p < .05$). Coronary vascular resistance fell significantly from 1.30 to 1.05 mm. Hg per 100 Gm. per min. ($p < .05$) (table 1 and fig. 2). The myocardial oxygen extraction declined from a mean of 12.7 volumes per cent to 11.2 volumes per cent (table 1). Since the fall in myocardial oxygen extraction was proportional to the rise in coronary blood flow, the myocardial oxygen usage was not significantly changed; the heart rate increased from an average of 87 before smoking to 93 afterwards (table 1). This rise was not so great as that usually reported in the literature, but because of apprehension the heart rate of most subjects was rapid even before the procedure was started.

The glucose extraction fell significantly from an average of 3.62 mg. per cent to 2.18 mg. per cent ($p < .05$) (table 2). This change was probably the result of the increased coronary blood flow, since glucose usage was not significantly increased. Myocardial pyruvate extraction fell, but the change was not statistically significant ($p > .05$) (table 2). Myocardial extraction of ketones rose after smoking, but not significantly ($p > .1$).

Discussion

Data reported in this paper illustrate that smoking results in a significant rise in the coronary blood flow and heart rate and a significant decline in the coronary vascular resistance and the myocardial extractions of oxygen and glucose. Average values of myocardial lactate and pyruvate extractions also fell, but the changes were not statistically significant. No change was recorded in the myocardial usage of foodstuffs and oxygen. The increase in coronary blood flow during smoking is in essential agreement with the observations of Mansfield and Hecht, Deitrich and Schimert, Bellet, and Schmitthenner.[11-13,16] These investigators worked with small doses of nicotine, either in pure form or as contained in tobacco smoke. The finding that cigarette smoking does not reduce coronary flow in normal individuals is in agreement with observations that electrocardiographic or ballistocardiographic changes are absent in individuals without coronary diseases.[22] However, on the basis of electrocardiographic or ballistocardiographic observations on patients with coronary heart disease, one may speculate that these individuals respond to smoking by a decrease in coronary blood flow and an increase in coronary vascular resistance. This assumption is borne out by the observations of Rinzler, who found that nicotine increased the coronary flow through a perfused normal rabbit's heart; when, however, the animal had previously been made atherosclerotic by a high cholesterol diet, nicotine resulted in a decline in flow through the perfused coronary vessels. No explanation on this different reactivity of the vessels has as yet been furnished.

Since the nitrous oxide method measures only over-all changes in coronary flow but records neither rapid nor phasic alterations, it is possible that a brief decline in coronary flow, induced by smoking, remained unrecognized. However, as ballistocardiographic or electrocardiographic alterations are not present in normal individuals during smoking, such a diminution in coronary flow is unlikely.

Summary

The effect of cigarette smoking on the coronary blood flow, myocardial oxygen consumption, and myocardial extraction of glucose, pyruvate, lactate, and ketones was followed in subjects without evidence of heart disease. Catheterization of the coronary sinus was performed to obtain coronary venous blood.

There was a significant rise in coronary blood flow and heart rate and a significant decline in coronary vascular resistance and myocardial extraction of oxygen and glucose.

These results indicate that cigarette smoking in normal subjects does not result in constriction of the coronary blood vessels.

Acknowledgment

The authors would like to acknowledge, with gratitude, the technical assistance of Mrs. Mona Barnett.

Summario in Interlingua

Esseva observate, in individuos sin signos apparente de morbo cardiac, le effecto del fumar de cigarrettas super le fluxo coronari de sanguine, le consumption myocardial de oxygeno, e le extraction myocardial de glucosa, pyruvato, lactato, e cetones. Catheterisation del sino coronari esseva executate pro obtener sanguine coronari-venose.

Esseva constatate un augmento significative del fluxo coronari de sanguine e del velocitate cardiac e un reduction significative del resistentia vascular coronari e del extraction myocardial de oxygeno e glucosa.

Iste resultatos indica que le fumar de cigarrettas non resulta, in subjectos normal, in le constriction del vasos coronari de sanguine.

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Warden, H. E., Read, R. C., DeWall, R. A., Aust, J. B., Cohen, M., Ziegler, N. R., Varco, R. L., and Lillehei, C. W.: Direct Vision Intracardiac Surgery by Means of a Reservoir of "Arterialized Venous" Blood. J. Thoracic Surg. **30:** 649 (Dec.), 1955.

An uncomplicated method is described that provides an adequate circulation of oxygenated blood to the vital organs of the body during the period of cardiac by-pass in patients undergoing operations within the open chambers of the heart. This is accomplished by a simple pump that simultaneously delivers blood from an arterial reservoir to the arterial system of the patient and withdraws an equal volume of venous blood from the vena caval system.

A simple method of obtaining blood possessing arterial chemical characteristics with which to supply the arterial reservoir is discussed. This can be done by utilizing the physiologic observation that blood drawn from a vein of an extremity that has been subjected to an external heat of 45 to 47 C. for 15 to 20 min. is arterialized. Thus, by preheating the arms of blood bank donors, relatively large quantities of arterialized venous blood can be collected with ease.

The first patient in which a high interventricular septal defect was repaired under direct vision using the described reservoir method of perfusion and arterialized venous blood is reported. This infant has made an uncomplicated recovery. The advantages of the method and the feasibility of its clinical application, especially to small patients, are discussed in detail.

MAXWELL

Chest Pain in Patients with Isolated Pulmonic Stenosis

By Richard P. Lasser, M.D., and Gabriel Genkins, M.D.

Chest pain like angina pectoris has been described in patients with pulmonary hypertension and cor pulmonale but its origin is obscure. In this article 5 patients are reported with isolated pulmonic stenosis and chest pain. On the basis of the clinical, electrocardiographic, hemodynamic, and pathologic findings the authors conclude that the chest pain is caused by ischemia of the right ventricular myocardium due to increased work and reduced coronary flow to the right ventricle.

THIS report concerns the occurrence of substernal and precordial chest pain in 5 patients with congenital stenosis of the pulmonic valve, a normal aortic root, and an intact interventricular septum. While not a commonly observed symptom in this particular congenital lesion nor frequently commented upon in the recent literature, chest pain and oppression are not at all rare in these patients and scattered reports can be found.[1-7] Laubry and Pezzi[8] in their text on congenital heart disease published in 1921 made note of chest discomfort in these patients terming the symptom "l'oppression d'effort" and distinguishing it from the dyspnea of effort. Stuckey,[9] in 1955, reported angina pectoris in 6 of 38 patients with isolated pulmonic stenosis. Other reports,[10-14] including several large series of cases, do not mention the occurrence of chest pain, nor is it mentioned in several of the texts on congenital heart disease.[15-17]

In this report on 5 patients with pulmonic stenosis and a normal aortic root who experienced chest pain, we will attempt to define its clinical characteristics, to discuss the hemodynamic conditions under which it occurs, to ascertain the probable site of origin, and to indicate its grave prognostic import.

The diagnosis of pulmonic valvular stenosis with a normal aortic root was made in all 5 patients by cardiac catheterization and was confirmed at the time of surgery in each. They were from the medical ward services of The Mount Sinai Hospital, New York. Cardiac catheterization was performed preoperatively. Pressures were recorded by means of direct needle puncture of the right ventricle and pulmonary artery at surgery. Data were obtained before and after valvulotomy. All pressures at operation were recorded simultaneously by means of Statham pressure transducers adjusted to equal sensitivity. Several of the patients were also recatheterized approximately 1 year after operation.

Surgical procedures were performed by Dr. Mark M. Ravitch, using a transventricular approach to the pulmonic valve.

Clinical Features

The pertinent data concerning clinical details, intracardiac pressures, and systemic oxygen saturations are shown in table 1 and will be discussed individually.

All of these patients had right ventricular systolic hypertension that equaled, surpassed, or closely approached systemic blood pressure. Diastolic pressure in the right ventricle was moderately elevated in 2 patients, markedly elevated in 1, and normal in the other 2.

The electrocardiogram revealed a pattern of right ventricular hypertrophy in all patients.

All of the patients were in their teens or older. This age grouping may be more apparent than real because of the difficulty in eliciting a clear history of some of the subtler aspects of pain from a younger child.

All of the patients had symptoms in addition to chest pain, with complaints ranging from exertional dyspnea or fatigue to frank right heart failure. These latter symptoms were not always prominent, however, and the primary complaint in 1 of the severe cases (R. D.) was

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TABLE 1.—*Clinical and Hemodynamic Data in Five Patients with Chest Pain and Isolated Pulmonic Stenosis*

Patient		Age	Pressure mm. Hg			Hgb. (Gm.)	O_2 Sat. (%)	Pain	Dyspnea	X-ray dilatation of P.A.
			RV	PA	Systemic†					
S.L.	Pre	20	105/5	30/15	120/90	16	91	+	++	++
	Post		53/5	25/10	130/90	14	94	0	±	
E.F.	Pre	36	160/22	Mean 0	100/60	14.0	92	+	0	+++
	*Post		72/22	39/15	90/60			0	0	
I.B.	Pre	16	96/6	14/5	136/73	12	99	++	+++	0
	*Post		51/8	21/11	90/60	12		0	+	
R.D.	Pre	35	134/10	—	130/70	16.0	97	+++	+	+
	*Post		84/9	36/13	90/60			0	0	
V.E.	Pre	52	129/3	Mean 6	151/88	14.0	94	++++	+++	++
	Post		114/8	25/8	140/90	14.0	95	0	+	

Pre = preoperative
Post = postvalvulotomy
* Pressures obtained in operating room.
† Systemic pressure obtained by direct needle puncture of femoral or brachial artery or at time of operation from the aortic arch.

chest pain alone, while in 2 other instances substernal oppression was the factor limiting activity.

Cardiac fluoroscopy demonstrated unequivocal right ventricular enlargement in all cases. Massive cardiomegaly was noted in only 2 patients, who had experienced frank bouts of congestive heart failure. In 1 of these instances the actual cardiac outline was difficult to delineate because of the presence of a moderate pericardial effusion.

Poststenotic dilatation of the main trunk of the pulmonary artery and its main left branch was of moderate degree in 3 patients, minimal in 1 other, and absent in the last. Postoperatively, the appearance of these vessels did not change noticeably although in all instances pain had been relieved by the surgical procedure.

Similarly, the presence, absence, or degree of peripheral arterial oxygen unsaturation was not proportional to the degree of pain experienced. Indeed, the 2 patients in whom lowered arterial oxygen saturation was noted (91 and 92 per cent) experienced the least severe pain of the group. In both instances it was thought that a right-to-left shunt existed via an interatrial communication.

Only 1 patient of our group (S. L.) was found to have polycythemia, and that was of a mild degree.

Characteristics of Chest Pain

S. L., a 30-year-old white woman with a known cardiac murmur since birth, had noted progressive exertional dyspnea since her early teens. For 3 months prior to admission she had suffered from distinct, rather severe substernal oppression, which did not radiate, was provoked by the mildest exertion, and was promptly relieved by rest. This sensation was distinct and different from dyspnea in that the latter was present almost constantly while the former occurred only on exercise with prompt relief by rest. The oppressive feeling was not true pain but might be described rather as a sensation on the verge of pain. Whether progression to a true anginal syndrome might in time have taken place is not known, as pulmonary valvulotomy completely abrogated the substernal oppression. The exertional dyspnea was, however, not significantly affected. In general, exercise tolerance improved significantly after surgery.

Symptomatology of such a nature would appear to correspond with "l'oppression d'effort" of Laubry and Pezzi.[8] It is an example of the mildest type of chest pain syndrome noted.

The second patient, E. F., a woman 36 years of age, complained of substernal oppression and burning brought on by exertion and relieved by rest. The duration of each episode was approximately 30 min. Again, these symptoms were separate and distinct from exertional dyspnea. The symptoms of exertional pain in this case were also completely relieved by valvulotomy.

The third patient, I. B., 16 years of age, described 2 distinct types of pain. Upon moderate exertion, she experienced a sharp, knife-like pain in the fourth

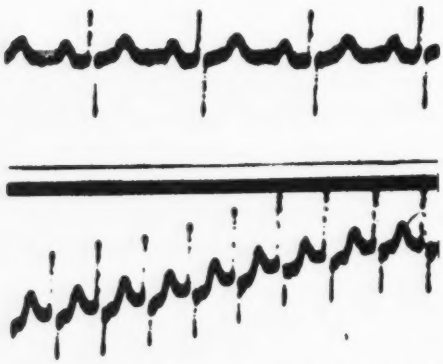

FIG. 1. R. D., the upper tracing shows an initial control electrocardiogram, standard lead II, at the beginning of cardiac catheterization. The lower tracing (also standard lead II) demonstrates the depression of S-T segment coincident with the supraventricular tachycardia and chest pain as described above.

left intercostal space that grew more intense on further exertion but was relieved rapidly by rest and nitroglycerin. Simultaneously, she would note a dull, heavy, constant substernal oppressive sensation that was more protracted and did not diminish as readily on resting. Nitroglycerin, however, always terminated both types of pain. These symptoms were completely eliminated by pulmonary valvulotomy.

R. D., a robust 35-year-old laborer, complained of severe precordial pain as his only symptom. For many years he had been aware of episodes of "fluttering" in the chest, occurring 1 to 6 times per year. These were at first accompanied by no symptoms other than slight dizziness that subsided spontaneously after 10 minutes to 1 hour. For the past 3 years, however, these episodes were accompanied by a severe burning precordial pain radiating to the neck and left arm that would cease approximately 1 to 2 hours after the conclusion of the attack. These episodes were felt to represent attacks of paroxysmal tachycardia. The sensation of dizziness became more severe and progressed at times to almost complete syncope. In addition, during the same period of time, the same type of pain was also noted to occur during periods of exertion at work. This pain was identical with that occurring during the bouts of palpitation. At all times rest would relieve the pain within 10 min. though a distinct substernal soreness might persist for 1 to 2 hours. For 1 year prior to admission, significant exertional dyspnea (1 flight, 10 blocks) had appeared. No manifestations of cardiac failure were noted.

During cardiac catheterization an episode of tachycardia was provoked by the exploring catheter tip and the full syndrome of substernal pain as well as electrocardiographic demonstration of myocardial ischemia were noted (fig. 1). Relief of the pain as well as freedom from prolonged bouts of tachycardia were brought about by transventricular valvulotomy although transient arrhythmias were present in the immediate postoperative course.

The fifth patient, V. E., a 51-year-old woman, was the most severely ill of all and experienced the greatest degree of disability from chest pain. For 1 year previously, she was greatly limited by severe precordial pain that appeared with effort and radiated to both shoulders and arms. It lasted about 15 min. and was followed by hours of precordial soreness. The severe pain was relievable by nitrogylcerin and had also been ameliorated by oxygen inhalation. One day prior to admission, she was stricken by an excruciating, crushing pain felt all over the anterior surface of the chest. This pain remained severe for about 6 hours and was finally relieved by analgesic injection. Residual soreness remained for several days. This attack had all the appearance of myocardial infarction, but failure of the electrocardiogram to develop characteristic changes, failure of sedimentation rate to rise, absence of fall in blood pressure, and the subsequent clinical course all made it extremely unlikely. It was finally considered that the attack represented severe and protracted coronary insufficiency. Pulmonary valvulotomy was done, a sufficient fall in right ventricular systolic pressure was effected, and after postoperative recovery had occurred, the chest pain was entirely relieved.

In summary then, 2 types of chest pain have been described by these patients. The first type is characterized by being (1) provoked by effort; (2) relieved by rest; (3) of variable duration, but generally less than 10 min.; (4) located either substernally or precordially; (5) of variable severity ranging from an oppressive sensation without true pain to severe pain without oppression; (6) experienced during tachycardia; (7) relieved by nitroglycerin.

The second type of pain is (1) protracted; (2) generally but not always provoked by effort; (3) not promptly relieved by rest; (4) of considerable severity occasionally simulating myocardial infarction; (5) relieved inconstantly by nitroglycerin or by oxygen inhalation.

Electrocardiographic Features

The electrocardiograms of these patients in all cases showed a pattern of marked and obvious right ventricular hypertrophy. All showed right axis deviation, a QRS complex of normal duration and the presence of V_1 of one of the forms of QRS complex associated with hypertrophy of the right ventricle. Three

patients showed a tall R wave and absent S wave in V_1. The R wave was either slurred or deeply notched on the upstroke. One patient showed an rsR′ complex in V_1, a pattern that is seen commonly in patients with right ventricular hypertrophy with or without conduction interference wherein the terminal R wave is taller than the initial one. One patient showed an Rs complex in V_1 with an R/S ratio of about 3:1. A marked depression of the S-T segments and inversion of T waves in precordial leads V_1–V_4 was noted in 1 patient (V. E.). This patient was the 1 of the group who experienced the most severe and protracted chest pain. Low or inverted T waves were found in standard lead II in 3 patients and in leads V_1–V_4 in 1 patient. None of the electrocardiographic findings mentioned were confined solely to this group of patients with right ventricular hypertrophy and chest pain. These same abnormalities of S-T segments and T waves were seen in other patients with marked hypertrophy of the right ventricle who may not have chest pain.

In the patient (V. E.) in whom electrocardiograms were taken during and after a protracted episode of chest pain, we did not observe parallel fluctuation of the depressed S-T segment corresponding with the clinical condition.

In another patient (E. F.) an electrocardiogram was obtained immediately following a short period of exercise (Master's single 2-step test). Because of fatigue and dyspnea, it was not possible to complete more than 1 min. of exercise, but chest pain was not provoked nor was a change observed in the electrocardiogram. A report of electrocardiograms taken after exercise in a series of 26 cases of pulmonic stenosis was published in 1954.[14] The authors found that very few changes were induced. The one observed chiefly was a shortening of the QTc interval. However, none of these patients was reported to have had chest pain, 15 were without any cardiac symptoms at all, another 9 showed only exertional dyspnea, 1 was in heart failure, and only 2 had markedly impaired exercise tolerance. Thus, most of these cases were examples of mild pulmonic stenosis or were in a stage of complete cardiac compensation.

One patient (R. D.), as previously demonstrated, did show electrocardiographic evidence of myocardial ischemia during a bout of supraventricular tachycardia that developed during cardiac catheterization. The electrocardiogram showed depression of the S-T segments during the tachycardia, which returned to normal following return to regular sinus rhythm. Electrocardiograms of 3 of these patients taken approximately 6 months to 1 year postoperatively, were available. The postoperative tracings were characterized by a distinct return to "normal." The right axis deviation was entirely absent in 1 and of much less extent in the other 2. The amplitude of the R wave in proportion to the S in V_1 diminished to an entirely normal relationship in 1 patient and to near normal in the others. Inversion of T waves has not reverted entirely to normal. An example is shown in figure 2.

Discussion

What is the site of origin of this chest pain and what is the mechanism of its production? We believe it to be due to myocardial ischemia. Further, the right ventricular myocardium is felt to be the ischemic site. Another possible source of pain that will be considered is the pulmonary artery itself. This structure has been considered to be responsible to atypical chest pain experienced by patients with idiopathic pulmonary hypertension and also in patients with chronic cor pulmonale[18] who present some clinical features in common with the group under discussion.

Evidence pointing to the probable existence of right ventricular myocardial ischemia has been derived from: (1) consideration of hemodynamic relationships and (2) pathologic findings.

Hemodynamic Considerations

The probable existence of right ventricular myocardial ischemia is indicated by the additive deleterious effects of an increased right ventricular myocardial oxygen demand in the presence of a hemodynamic state that is unfavorable to coronary flow to the right ventricle. The increased oxygen demand results from a greatly hypertrophied right ventricular myocardium, which is an anatomic expression

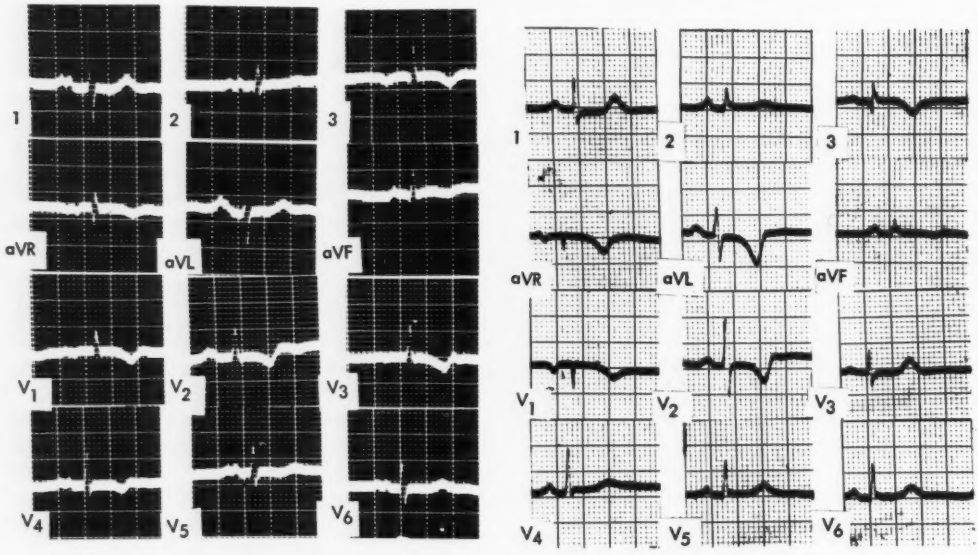

FIG. 2. E. F., preoperative (December 12, 1954, left) and postoperative (March 21, 1955, right) electrocardiograms. Note diminished amplitude and more normal contour of P waves; disappearance of right axis deviation, of the late R wave in aV_R, and tall R wave in V_1, reflecting the change to normal from right ventricular preponderance.

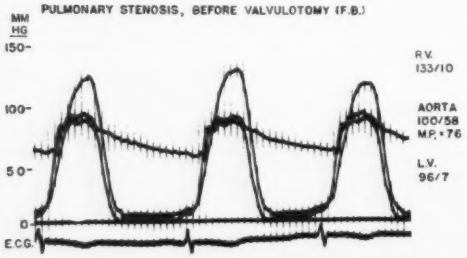

FIG. 3. F. B., Simultaneous needle punctures of pertinent areas, recorded by means of strain gages adjusted to equal sensitivity, at time of operation. Note that right ventricular pressure exceeds aortic pressure from the onset of aortic ejection to .04 sec. beyond closure of the aortic valves.

of the high level of right ventricular work, about 5 times that of the normal right ventricle in patients of this type.[19]

Factors acting to impair coronary circulation are as follows:

1. The marked elevation of right ventricular intracavity pressure during ventricular systole and the protracted duration of this period by comparison with events in the aorta. This pressure relationship is unfavorable to *right* ventricular coronary flow by virtue of its influence upon intramural perfusion. Perfusion of ventricular musculature during its contraction proceeds when a difference exists between aortic pressure, which acts to drive flow forward, and the pressure that is exerted on the intramural coronary vessels by muscular contraction, which opposes flow by compressing the vascular lumina. Since the intramural pressure is roughly equivalent to the intracavity pressure,[20] it is evident that intramural perfusion of the right ventricle (particularly of the innermost layers) is probably substantially prohibited during much of right ventricular systole when the right ventricular pressure exceeds the aortic pressure. These pressure-time relationships between aorta and right ventricle are illustrated in figure 3. The curves were obtained by direct needle puncture at the time of operation according to a technic previously reported.[21] This patient had isolated pulmonic valvular stenosis with a moderate degree of congestive failure but did not complain of distinct chest pain or oppression.

2. A low level of systemic cardiac output which is relatively fixed and cannot be augmented in a normal fashion during exercise.[9, 17]

3. The presence of a moderate to marked elevation of right atrial and ventricular diastolic pressure. This factor acts to reduce both the coronary arteriovenous pressure gradient and Thebesian vein drainage, thus increasing the intravascular resistance to flow during diastole.[22] Though direct measurement of right coronary flow has not been accomplished in man, experimental work in dogs has specifically demonstrated myocardial ischemia and reduced coronary flow in the presence of right ventricular systolic hypertension such as that produced by acute narrowing of the pulmonary artery or mitral valve orifice.[23-25]

An insight into the compensatory mechanisms of the heart is afforded by the observations that in dogs the immediate effect of elevation of right ventricular systolic pressure is actually an increase in right coronary arterial flow.[26] When the experimental lesion is maintained for a few hours, however, coronary flow consistently diminishes below the resting level. Gregg[27] has explained those findings as follows: "Thus in the latter stages of an experiment . . . the *flow-reducing effect* of increased extravascular support [intramural tension] is dominant over whatever flow-promoting mechanism the heart has retained, and would appear to be left almost unopposed by any concomitant dilatation of the coronary bed."

It is obvious that the human heart, too, is able for many years to compensate for these various factors that reduce coronary perfusion and increase the myocardial oxygen demand. Finally, some new factor intervenes, such as tachycardia, or further reduction of the coronary flow and increase in the degree of hypertrophy exceed the limits of coronary compensation and symptoms of angina or signs of congestive failure appear.

Pathologic Findings

Pathologic examination of postmortem specimens has furnished direct evidence of the prior existence of a diffuse right ventricular myocardial ischemia. A review of 5 cases of patients with severe, isolated pulmonic stenosis revealed extensive fibrosis of a patchy nature distributed throughout the right ventricle. The left ventricle was spared, indicating that the coronary insufficiency was not ubiquitous but was rather confined to the right ventricular myocardium. The most severe example of this pathologic lesion is shown in figure 4. These

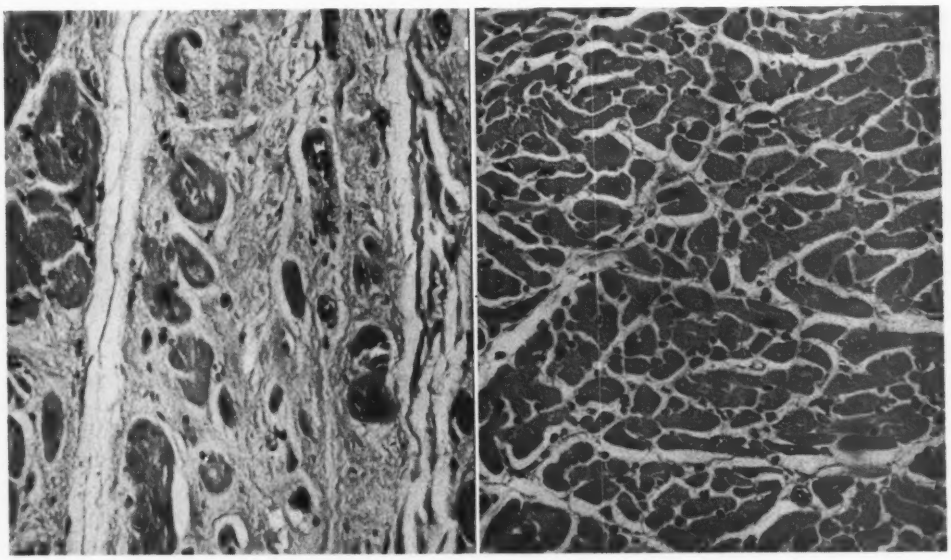

FIG. 4. A. L., Right (left) and left (right) ventricular sections (both × 260) revealing the severe right ventricular myocardial scarring, and a normal appearing left ventricular myocardium.

sections were obtained from a 21-year-old white man, A. L., who was found at postmortem examination to have combined pulmonary valvular stenosis and infundibular stenosis with intact ventricular septum and interatrial septal defect. He had died as a result of the rupture of a frontal lobe brain abscess. Marked exercise intolerance had been noted for many years but no history of chest pain was obtained.

The right ventricular myocardium was 2.5 cm. in thickness, exceeding the thickness of the left ventricular wall. Grossly, the right ventricular myocardium revealed marked fibrosis in contrast to a normal appearing left ventricular musculature. The extent of this difference was strikingly illustrated by the representative areas of the 2 ventricles in figure 4. There was mild right coronary artery preponderance. No coronary sclerosis was observed. This extensively scarred right ventricular myocardium would certainly seem to be a site of chronic coronary insufficiency. Other investigators have reported similar pathologic findings in these patients.[28-30]

The presence or absence of anginal pain, then, in any 1 individual patient might be a function of the acuteness with which local anoxia occurred under stress. Somewhat similar type of chest pain has been reported in patients with pulmonary hypertension due to various causes including idiopathic pulmonary hypertension,[31] chronic pulmonary fibrosis and emphysema,[18, 32] and mitral stenosis.[33, 34] Viar and Harrison[18] have proposed that chest pain in these patients is not due to myocardial ischemia but has its origin in the distended pulmonary artery trunk itself. Is it possible that such a hypothesis applies to the cases reported here? In our cases of pulmonic stenosis, the main and initial branches of the pulmonary artery are dilated, often considerably, but the one essential element of pulmonary hypertension is lacking. Actually, the pressure within the pulmonary artery is at normal or lower than normal levels.

Is it possible then that poststenotic dilatation of the pulmonary artery alone is capable of giving rise to pain? Certainly, at operation these pulmonary arteries are not flaccid but are seen to be tense and distorted by the impact of a jet stream of blood from the right ventricle ejected under considerable force. Pain that is localized to the site of an aneurysmal dilatation of either the aorta or pulmonary artery secondary to syphilitic vasculitis is well known. On the other hand, patients with only moderate degrees of pulmonary stenosis may have pronounced dilatation of the pulmonary artery and in our experience do not experience chest pain. In our group, as mentioned, there was no correlation whatever between the size of the pulmonary artery and the severity of chest pain.

Summary

A group of 5 patients with proved isolated pulmonic valvular stenosis manifested anginal pain of varying severity, ranging from mild substernal oppression to severe, intractable precordial pain. In all cases, the diagnosis was proved at catheterization and in each instance the symptomatology was completely relieved by surgical intervention.

The right ventricular myocardium is thought to be the source of this anginal pain. This concept is analyzed through electrocardiographic, hemodynamic, and pathologic data. It is pointed out that this cardiac lesion requires the right ventricle to labor under a strikingly increased stroke work load, under hemodynamic circumstances that are unfavorable to coronary flow. Under stimulus of effort or in the presence of arrhythmias these difficulties are enhanced and clinical and electrocardiographic evidence of myocardial insufficiency may be noted.

Pathologic evidence of severe right ventricular myocardial fibrosis was demonstrated in a patient with pulmonic stenosis who died of an unrelated cause.

The syndrome of "right-sided" angina may prove to be of prognostic significance in these patients with pulmonic stenosis, as its appearance would seem to herald an imbalance between the demands made on and the resources of the right ventricular myocardium. It would seem logical to apply this concept to other cardiac lesions, congenital or acquired, that have led to right ventricular hypertension and hypertrophy.

Summario in Interlingua

Un gruppo de 5 patientes con provate stenosis pulmono-valvular isolate manifestava dolores anginal de varie grados de severitate, ab leve oppression substernal usque a sever e intractabile dolores precordial. In omne casos le diagnose esseva confirmate per catheterisation, e in omne casos le symptomatologia esseva completemente alleviate per le intervention chirurgic.

Nos opina que le myocardio ventricular es le fonte del dolor anginal. Iste conception es analysate super le base de datos electrocardiographic, hemodynamic, e pathologic. Es signalate que iste lesion cardiac require ab le ventriculo dextere que illo labora sub un fraffantemente augmentate carga de labor pulsatile e sub conditiones hemodynamic que es disfavorabile al fluxo coronari. Le stimulo de effortio o le presentia de arrhythmias resulta in un augmento de iste difficultates, e manifestationes clinic e electrocardiographic de insufficientia myocardial deveni observabile.

Signos pathologic de sever grados de fibrosis myocardial dextero-ventricular esseva demonstrate in un patiente con stenosis pulmonic qui moriva ab un causa sin relation al condition hic discutite.

Le syndrome de angina "dextero-lateral" pote esser de signification prognostic in iste patientes con stenosis pulmonic, proque su manifestation pare annunciar un disbalancia inter le demandas que le myocardio dextero-ventricular deberea satisfacer e le ressources que illo possede. Il pare logic applicar iste concepto a altere lesiones cardiac, congenite o acquirite, que ha resultate in le disveloppamento de hypertension e hypertrophia dexteroventricular.

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Two hundred thirty-one euthyroid, seriously ill cardiac patients have been treated with radioactive iodine since February 1950. Of particular interest is the analysis of the original 100 patients treated 4 years ago. The patients in this series were treated for severe angina pectoris or severe congestive heart failure, or a combination of both. The rationale of treatment was to produce a state of beneficial relative hypothyroidism by lowering the total metabolism of the body so that the heart had less work to do. An interesting feature in this series of cases was the use of "thyrogram" (a diagram of the thyroid gland made by a scintillation counter) to check gland size and function. Fifty-six per cent of 94 patients with angina pectoris showed excellent results, and 37 per cent of this number showed good results. Of 78 patients with congestive heart failure 53 per cent showed excellent and 28 per cent good results. A group of 59 patients with angina pectoris and congestive heart failure combined showed 48 per cent excellent and 32 per cent good results.

KITCHELL

Immunologic Evidence of Group A Streptococcal Infection in Patients Undergoing Mitral Commissurotomy

By Gene H. Stollerman, M.D., William F. Lynch, M.D., Mario A. Dolan, M.D., Dennison Young, M.D., and John B. Schwedel, M.D.

Serum levels of 3 group A streptococcal antibodies were determined in 53 patients prior to mitral commissurotomy and monthly for 3 to 6 months postoperatively. Significant elevation of antibody titers was relatively infrequent prior to commissurotomy and the presence of chronic productive inflammatory lesions in the biopsied atrial appendage was usually unrelated to recent streptococcal infection. The "postcommissurotomy syndrome" also occurred in some patients without evidence of such infection. Postoperative subclinical streptococcus infection occurred frequently enough, however, to suggest the need for vigorous preoperative penicillin therapy and careful postoperative prophylaxis.

RELATIVELY little information is available concerning the relationship of intercurrent infection with group A streptococci to the natural history of rheumatic heart disease in the adult. Typical Aschoff lesions in the biopsied atrial appendage of patients who have undergone mitral commissurotomy have been observed frequently.[1] This finding is often unrelated to the functional state of the myocardium in such patients and may be present without other clinical manifestations of rheumatic fever or laboratory tests indicative of systemic inflammation.[2] The factor of recent streptococcal infection as a possible contributing cause to the chronicity of these lesions has been considered but has not been studied extensively.

Furthermore, certain postoperative complications of mitral commissurotomy have been interpreted as traumatic "reactivation" of rheumatic fever.[3] Whether or not the so-called "postcommissurotomy syndrome" represents an exacerbation of rheumatic inflammation remains problematic. Information concerning the factor of streptococcal infection in patients with this complication is also scarce.

It is possible to detect streptococcal infection with a high degree of accuracy, even when the disease is asymptomatic. Quantitative immunologic methods for the measurement of antistreptolysin O (ASO), antistreptokinase (ASK), and antihyaluronidase (AH) have revealed an increase in the serum concentration of at least one of these specific antibodies in more than 95 per cent of patients infected with group A streptococci.[4]

In the study reported here, determinations of these 3 antibodies were made in the sera of 53 patients subjected to mitral commissurotomy and biopsy of the atrial appendage. The data have been analyzed with particular reference to histopathologic evidence suggestive of rheumatic carditis and to the development of the so-called postcommissurotomy syndrome.

Methods

Fifty-three patients were studied who were admitted to Montefiore Hospital for mitral commissurotomy and medical management by the cardiovascular research team of that institution. Immunologic studies were made in the laboratories of Irvington House. Samples of blood were obtained by venipuncture prior to commissurotomy and at monthly intervals postoperatively for a period of 3 to 6 months. Sera were separated and stored at −20 C.

At the end of the follow-up period the stored samples of serum obtained from each patient were assayed simultaneously to evaluate more accurately variations in antibody titer. By this method an increment of 2 tubes in the dilution schedules employed was considered a significant rise in titer.

Antistreptolysin serum titers were measured by

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Supported in part by Grant H-903(C), National Heart Institute and by the Westchester Heart Association and the Masonic Foundation for Medical Research and Human Welfare.

TABLE 1.—*Distribution of Streptococcal Antibody Titers in Relation to the Histopathology of the Auricular Myocardium Biopsy in Fifty-three Patients Undergoing Mitral Commissurotomy*

Antibody	Number patients with titers in the range of:			
	0–100 U./ml.	100–200 U./ml.	201–333 U./ml.	400 and over
Antistreptolysin O				
No lesions*	26	10	1	0
Lesions†	10	4	2	0
Total	36	14	3	0
Antihyaluronidase				
No lesions	30	7	0	0
Lesions	10	4	2	0
Total	40	11	2	0
Antistreptokinase				
No lesions	30	3	3	1
Lesions	11	4	1	0
Total	41	7	4	1

* Absence of inflammatory lesions.

† Presence of typical Aschoff nodules or other inflammatory lesions suggestive of chronic rheumatic carditis.

TABLE 2.—*Per Cent of Patients with Antibody Titer >200 U./ml. at Months Indicated from Onset of Rheumatic Fever*[4]

Antibody	1 month	2 months	6 months	12 months
Antistreptolysin O	95	73.5	33.9	20
Antihyaluronidase	70	67.6	32.2	25
Antistreptokinase	70	52.8	86	19
Any 1 of 3 antibodies	95	94.1	52.7	38.6
No. patients studied	20	68	59*	44*

* Represents same patients studied during the first or second months.

the method of Rantz and Randall[5] with minor modifications. Antistreptokinase was measured by the method of Christensen,[6] and determination of antihyaluronidase titers was made by the turbidimetric method of Harris and Harris.[7] A culture of the throat was made at each follow-up visit whenever possible; in many instances, however, this was not done. Many patients were under the care of private physicians postoperatively and were distributed widely geographically. In such cases serum samples were forwarded to our laboratory.

The biopsy of the atrial appendage was examined in the Department of Pathology at Montefiore Hospital and classified according to certain histopathologic criteria. Specimens with inflammatory lesions suggestive of rheumatic carditis were divided into those containing characteristic Aschoff nodules and those in whom such lesions were absent but other histologic manifestations suggested rheumatic inflammation. Such lesions were characterized by focal interstitial necrosis of the myocardium or focal fibrosis associated with clusters of cellular infiltrates, usually mononuclear in type and of the lymphocytic variety.

During the postoperative period an attempt was made to maintain some form of continuous prophylaxis against new streptococcal infection. This was possible in about 60 per cent of patients. In the remainder, prophylactic medication was not administered routinely by the physicians attending the patients. The prophylactic regimens employed consisted of one of the following: A single monthly injection of 1.2 million units of benzathine penicillin; 200,000 units of penicillin G orally daily; or a single daily oral dose of 1.0 Gm. of sulfadiazine.

Criteria for the diagnosis of the "postcommissurotomy syndrome" consisted of the following: an afebrile, relatively asymptomatic postoperative interval of at least 2 weeks, followed by the abrupt appearance of fever and chest pain, with or without objective evidence of pericarditis or pleuritis, and often associated with increased manifestations of congestive heart failure, or with polyarthralgia. These criteria were not always sharply defined and in general the diagnosis was limited to those patients with findings most characteristic of the syndrome described above (table 4).

RESULTS

General Distribution of Titers. The distribution of antibody titers of the sera obtained from patients on admission to the hospital, and shortly before commissurotomy, is shown in table 1. In general, the titers of the 3 antibodies were predominantly quite low and all 3 followed the same pattern of distribution. The sera of only 3 patients (5.7 per cent) were above 200 U. per ml. in ASO titer, and none was above 333 U. per ml. The results were virtually the same with respect to the antihyaluronidase and antistreptokinase titers. Forty-three patients (81 per cent) showed titers of less than 200 U. per ml. in all 3 antibodies measured in the serum obtained at the initial bleeding, prior to commissurotomy.

For purposes of comparison, the data in table 1 may be related to those of a previous study[4] of the behavior of the same antibodies in patients during the first year of recovery from an attack of acute rheumatic fever (table 2). The percentage of patients with titers that remained greater than 200 U. 1 year after an acute rheumatic attack, without

intercurrent streptococcal infection, was higher than that found in the mitral commissurotomy group.

Relationship of Preoperative Antibody Titers to Inflammatory Lesions in the Auricular Biopsy. The data are further subdivided between those patients whose auricular biopsies revealed evidence suggestive of rheumatic inflammation and those with no such lesions (table 1). There were 16 patients of the 53 studied whose biopsy showed inflammatory lesions. In these the distribution of antibody titers was not significantly different from the group without such lesions. Eight of the 16 patients had lesions containing typical Aschoff nodules. The distribution of antibody titers in these was not significantly different from patients with lesions less characteristic of rheumatic fever.

Patients with a Postoperative Rise in Antibodies. There were 14 patients (26 per cent) who showed a significant rise in at least 1 of the 3 antibodies measured sometime during the 6-month postoperative period of observation. Four of these showed a rise in the antihyaluronidase titer alone; 1 showed a rise in the ASO titer alone. The remaining 9 showed a rise in at least 2 of the 3 antibodies (table 3). Seven of these 14 patients received no prophylaxis, and 4 did not receive prophylaxis until respiratory symptoms or a febrile episode occurred. The remaining 3 received what was considered "adequate" prophylactic treatment. Ten of the 14 patients manifested an antibody rise within 1 month of the date of operation. Four of the 14 patients developed the postcommissurotomy syndrome (table 3).

Patients with the Postcommissurotomy Syndrome. There were 9 patients who developed signs and symptoms suggestive of the "postcommissurotomy syndrome" (table 4). Almost all had chest pain and fever as presenting symptoms following a "latent period" of at least 2 weeks from the operative date. Two patients had an exacerbation of the symptoms and signs of congestive heart failure in addition to chest pain and fever. Two others had mild symptoms of polyarthritis and 1 had vague polyarthralgia.

There was no immunologic or other evidence

TABLE 3.—*Patients with Postoperative Increase in Antibodies*

Patient	Increase in antibody (log titer)			Postcommissurotomy syndrome
	ASO	AH	ASK	
1. A. C.	0.7	0	0.6	+
2. L. Vs.	0.3	0.3	0	0
3. E. E.	0.1	0.45	0	+
4. D. F.	0	0.6	0	0
5. F. C.	0.4	0.4	0.6	0
6. J. B.	0.1	0.45	0	+
7. A. G.	0.4	0.3	0	0
8. E. F.	0	0.45	0	0
9. E. M.	0.3	0.3	0.3	0
10. I. K.	0.6	1.2	0.3	0
11. J. K.	0.8	0.6	0	0
12. L. W.	0.2	0	0	0
13. A. S.	0.3	0.3	0.3	0
14. C. S.	0.7	0.6	0.9	+

TABLE 4.—*Patients with Postcommissurotomy Syndrome*

Patient	Lag period (weeks)	Chest pain	Fever	Increased congestive failure	Joint manifestations	Streptococcal antibodies		
						Low†	High‡	Rise§
1. R. B.	3	+	+	0	0	+	0	0
2. I. B.	9	0	+	0	Polyarthritis	+	0	0
3. M. E.	2	+	0	0	0	+*	0	0
4. M. C.	8	+	+	+	0	0	+	0
5. F. C.	9	+	+	0	0	0	+	0
6. E. E.	5	+	+	0	Polyarthralgia	+	0	+
7. C. S.	4	+	+	+	0	+	0	+
8. A. C.	26	+	+	0	Polyarthritis	+	0	+
9. J. B.	10	+	+	0	0	+	0	+

* Rapid fall ASK 160 → 20.

† ASO, AH, and ASK all below 200 U./ml. preoperatively.

‡ At least 1 of 3 antibodies greater than 200 U./ml. preoperatively.

§ Rise in at least 1 antibody during postoperative period.

TABLE 5.—*Patients with Histopathologic Evidence of Carditis in Auricular Myocardium*

With Aschoff nodules	Streptococcal antibodies			Postcommissurotomy syndrome
	Low*	High†	Rise‡	
1. C. R.	+	0	0	0
2. M. E.	+	0	0	+
3. N. R.	+	0	0	+
4. M. O.	+	0	0	0
5. G. T.	0	+	0	0
6. W. R.	0	+	0	0
7. A. C.	+	0	+	+
8. I. K.	+	0	+	0
Without Aschoff nodules				
1. E. L.	+	0	0	0
2. O. S.	+	0	0	0
3. M. S.	+	0	0	0
4. C. H.	0	+	+	0
5. L. S.	0	+	0	0
6. E. M.	+	0	+	0
7. F. C.	+	0	+	0
8. L. Vs.	+	0	+	0

* ASO, AH, and ASK all below 200 U./ml. preoperatively.

† At least 1 of the 3 antibodies greater than 200 U./ml. preoperatively.

‡ Rise in at least 1 antibody during postoperative period.

TABLE 6.—*Streptococcal Immune Response in Patients Undergoing Mitral Commissurotomy*

Patient group	Total in each group	Carditis histopathologically		Postcommissurotomy syndrome
		With Aschoff nodules	Without Aschoff nodules	
Low antibody* levels Pre- and Postop.†	29	4	3	3
High antibody Levels Preop.‡	10	2	2	2
Rise in antibody levels Postop.§	14	2	3	4
Totals	53	8	8	9

* Antibodies measured: Antistreptolysin O, Antistreptokinase, Antihyaluronidase.

† ASO, AH, and ASK all below 200 U./ml. preoperatively.

‡ At least 1 of the 3 antibodies greater than 200 U./ml. preoperatively.

§ Rise in at least 1 antibody during postoperative period.

of recent streptococcal infection in the first 2 patients listed in table 4. The 3 antibodies were all below 200 U. before the operation and remained low during the entire postoperative period. The third patient was similar except for a rather rapid fall in ASK titer from 160 to 20 U. per ml. during the postoperative period, a finding suggesting a mild streptococcal infection sometime before admission to the hospital for commissurotomy. The fourth and fifth patients had high initial preoperative antibody titers but showed progressive fall or no change in titer during the postoperative period. The remaining 4 patients had low titers initially but showed a significant rise in one or more antibodies during the postoperative period.

It should be noted that 1 patient (A. C.) developed fever, polyarthritis, and vague chest pain as long as 6 months after operation and showed a marked rise in ASO from 50 U. preoperatively to 250 U. 2 months postoperatively. The ASK titer rose simultaneously from less than 20 U. to 80 U. This patient also had typical Aschoff nodules in the myocardium of the biopsied auricle. Aside from this case, the others all developed their symptoms within 2 to 10 weeks after operation.

Of the 9 patients listed in table 4, only 3 had histologic evidence of rheumatic inflammation in the auricular myocardium (table 5). Of these, only the one patient mentioned above (A. C.) had evidence of antecedent streptococcal infection. Table 5 indicates a lack of definite correlation between histologic findings in the auricular myocardium, recent streptococcal infection, and the postcommissurotomy syndrome. This is further indicated by the analysis of the data in table 6, which relates the incidence of histopathologic findings and the postcommissurotomy syndrome to each of 3 patient groups: those with low antibody levels preoperatively and postoperatively, indicating no recent streptococcal exposure; those with initially high antibody titers, indicating relatively recent preoperative infection; and those with postoperative rise in antibody titer.

Tests for the presence of C-reactive protein (CRP) were made on sera obtained from all

patients prior to commissurotomy. CRP was absent from the sera of 3 of the 16 patients later found to have histologic myocardial lesions in the atrial appendage, confirming the previous observations that a negative test for this protein does not exclude the presence of such lesions.[8]

Discussion

The data presented indicate that histologic evidence of chronic productive inflammatory lesions in the auricular myocardium of patients undergoing mitral commissurotomy is not usually associated with recent streptococcal infection. These findings would support the concept that such lesions are the lingering traces of a very low grade chronic inflammatory process rather than recent exacerbations of the disease due to antecedent streptococcal infection.[9, 11] This interpretation is consistent with the clinical observations that such lesions appear to bear little relationship to the functional state of the myocardium and do not correlate with the degree of heart failure or the patient's subsequent course following commissurotomy.[2, 10] The antistreptolysin determinations are also in agreement with such determinations as have been made in other reported series.[2, 11, 12]

This study sheds little light upon the pathogenesis of the postcommissurotomy syndrome. This ill-defined syndrome appeared to have no consistent relationship to antecedent streptococcal infection; indeed, in at least 2 patients such infection could be virtually excluded, both preoperatively and postoperatively. However, 4 of the 9 patients with the syndrome had a postoperative rise in at least 1 antibody (table 3). This poses the question whether their symptoms represented reactivation of rheumatic fever as a result of subclinical streptococcal infection. This possibility appeared likely in 1 patient (A. C.) whose exacerbation occurred 6 months after operation and was accompanied by frank polyarthritis and a marked rise in antistreptolysin O and antihyaluronidase. She was included in the "postcommissurotomy syndrome" group because her clinical findings met the criteria outlined in the protocol for this study. In the remaining patients the clinical syndrome was much less sharply defined and the symptoms of chest pain were much more difficult to dissociate from direct sequelae of surgical trauma.

The relative frequency (26 per cent) with which a significant rise in antibody titers occurred postoperatively deserves special comment, particularly since half this group received some type of prophylaxis considered to be more or less satisfactory. Ten of the 14 patients developed a rise in antibody within 1 month of operation. This suggests that infection occurred most often during the immediate postoperative period. This result is somewhat surprising inasmuch as most patients received large parenteral doses of penicillin postoperatively, but not, however, in any systematic fashion. Nor was a concerted effort made preoperatively to clear hemolytic streptococci from the respiratory tract by a preliminary course of penicillin, a procedure that, in retrospect, may be justified, even though pharyngeal throat cultures may fail to reveal the presence of these organisms. It would be of interest to determine whether the specific antibody elevations observed postoperatively in this series can be prevented by intensive preoperative treatment with a 10-day course of penicillin followed by careful postoperative prophylaxis with regular parenteral injections of benzathine penicillin, a method that has proved highly effective in patients recovering from acute rheumatic fever.[13] Some justification for this point of view is the frequency with which group A streptococci have been recovered from excised tonsils of adults when throat cultures of the intact mucosa have been negative.[14]

Finally, the relative infrequency with which recent streptococcal infection was observed in the group as a whole prior to commissurotomy is not, in the authors' opinion, justification for regarding antistreptococcal prophylaxis as unnecessary in the adult rheumatic cardiac. Although streptococcal infection is likely to be less frequent in this age group than in childhood and adolescence, it has not been determined whether the adult with rheumatic heart disease loses the heightened propensity to develop rheumatic recurrences following a streptoccal infection that has been observed in pa-

tients with rheumatic fever during the first several years of convalescence.

Summary

The serum titers of 3 streptococcal antibodies, antistreptolysin O, antistreptokinase, and antihyaluronidase, were determined in 53 patients with mitral stenosis prior to mitral commissurotomy and monthly postoperatively for 3 to 6 months.

Forty-three patients (81 per cent) had serum titers of less than 200 U. per ml. in all 3 antibodies prior to commissurotomy. The distribution of the titers of all 3 antibodies was lower than that observed in patients free of streptococcal infection for 1 year following acute rheumatic fever.

In 16 patients whose auricular myocardial biopsy revealed histologic lesions of chronic myocarditis, the distribution of antibody titers was no different from that of the patients with no such lesions.

Fourteen patients developed an increase in the titer of at least 1 antibody during the 6-month postoperative period. In 10 of these the rise occurred within a month of the operation.

Nine patients developed the "postcommissurotomy syndrome." In 4 of these there was an increase in antibody postoperatively. In 2 there was no immunologic evidence of streptococcal infection preoperatively or postoperatively. The remaining 3 had either elevated or rapidly decreasing antibody titers prior to operation. There was no consistent correlation between the presence of this syndrome, the presence of histologic evidence of myocarditis, and the behavior of streptococcal antibodies.

The data suggest that histologic evidence of persistent chronic rheumatic carditis in the atrial appendage of patients subjected to mitral commissurotomy is usually unrelated to recent streptococcal infection and that the "postcommissurotomy syndrome" may also occur without such infection. The apparent high incidence of postoperative subclinical streptococcus infection observed in this study is noteworthy, however, and suggests the need for vigorous preoperative penicillin therapy and postoperative prophylaxis.

Summario in Interlingua

Le titros seral de 3 anticorpores streptococcal —antistreptolysina O, antistreptocinase, e antihyaluronidase—esseva determinate in 53 patientes con stenosis mitral ante commissurotomia mitral e post le operation a intervallos mensual durante periodos de 3 a 6 menses.

Quaranta-tres patientes (81 pro cento) habeva titros seral de minus que 200 unitates per ml pro omne le 3 anticorpores ante le commissurotomia. Le distribution del titros de omne 3 anticorpores esseva plus basse que illo observate in patientes qui habeva essite libere de infection streptococcal durante 1 anno post acute febre rheumatic.

In 16 patientes, in qui le biopsia auriculo-myocardial habeva revelate lesiones histologic de myocarditis chronic, le distribution del titros de anticorpore non differeva ab illo trovate in patientes sin tal lesiones.

Dece-quatro patientes disveloppava un augmento del titro de al minus un del anticorpores durante le periodo de 6 menses post le operation. In 10 de iste casos, le augmento occurreva intra un mense post le operation.

Le disveloppamento del "syndrome post-commissurotomic" esseva notate in 9 patientes. In 4 de istes il habeva un augmento del anticorpores post le operation. In 2 casos il habeva nulle indication immunologic de infection streptococcal ante o post le operation. Le remanente 3 patientes habeva elevate o rapidemente decrescente titros de anticorpore ante le operation. Il non existeva un uniforme correlation inter le presentia de iste syndrome, le presentia de indicationes histologic de myocarditis, e le comportamento de anticorpores streptococcal.

Le datos suggere que signos histologic de persistente chronic carditis rheumatic in le appendice atrial de patientes subjicite a commissurotomia es usualmente sin relation a recente infectiones streptococcal e que mesmo le syndrome post-commissurotomic pote occurrer sin tal infectiones. Le apparentemente alte incidentia de subclinic infectiones streptococcal postoperatori que esseva observate in iste studio es digne de attention e suggere le necessitate de un energic therapia pre-operatori a penicillina e de mesuras prophylactic post le operation.

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The presence of 5-HT (serotonin) has been demonstrated in many body tissues and fluids of man and animals. It has been suggested that this substance plays a part in hemostasis and in the regulation of vascular tonus. In an attempt to define the mechanism of such a role, 5-HT was infused into the human brachial artery. With doses of more than 1 μg./min., the forearm and hand blood flow decreases, the volume increases (plethysmography) and there is a marked flushing of skin. These results demonstrate constriction of those vessels that control the rate of blood flow (the arterioles) and at the same time dilate the minute vessels of the skin. The observations lend support to the theory proposed by others that the clinical triad of carcinoid tumor, pulmonary stenosis, and red-blue color of the skin associated with periodic attacks of intense flushing is due to increase in substances resembling 5-HT in the blood.

AVIADO

Effects of Meals of Different Fats on Blood Coagulation

By Ancel Keys, Ratko Buzina, Francisco Grande, and Joseph T. Anderson

Previous work has shown that a high-fat meal produces an increased coagulability of the blood. This fact is of interest in view of the effects of dietary fat on the serum cholesterol and its association with coronary disease. Since fats containing large amounts of unsaturated fatty acid tend to reduce the serum cholesterol rather than increase it, it is important to examine the effects of fats with different fatty acid composition on blood coagulation. Comparisons are presented of the effect on blood coagulability of feeding butterfat, corn oil, hydrogenated coconut oil, and a marine fish oil.

RECENTLY we reported on the increased coagulability of blood after a fat meal.[1] That the effect was due to the ingested fat was shown by the fact that no shortening of the coagulation time occurred in the same individuals after eating a nonfat meal of equal caloric content or after continuing fasting. In fact, in both these conditions the coagulation time tended to be slightly prolonged in comparison with the control (pre-meal) blood sample.

Materials and Methods

Fats. In previous experiments we used butterfat and the question arose as to whether other fats provoke a similar response. The present paper presents the findings from a new series of experiments with corn oil, hydrogenated coconut "oil" (actually a soft solid), and sardine oil as well as with butterfat. These oils were selected to represent great diversity in the constituent fatty acids. In terms of degree of saturation of the fatty acids, the experimental fats and oils range from hydrogenated coconut oil (Hydrol*) with an iodine number (Hanus) of 2.5 to sardine oil with a value of 185. The iodine numbers of butterfat and of corn oil are 38 and 120 respectively.

Subjects. Twelve schizophrenic men aged 35 to 60 years were subjects in 5 experiments, 1 with each of the 4 fats and 1 with a carbohydrate meal. They were long-time patients in the Hastings State Hospital but were physically healthy and considered to be metabolically "normal." All of them were cooperative, stabilized in their mental illness, and were accustomed to venepunctures. Four of the men had been subjects in the previously reported studies with butterfat. Before and between experiments they subsisted on the standard diet of the hospital, which provides, on the average, about 40 per cent of the calories in the form of fats and is in other respects similar to average "good" American diets.

Procedure. The experiments were started in the morning. The men had their usual meals the night before and they arose and made their toilets but breakfast was withheld. They walked slowly to the metabolic laboratory where they spent the next 6 or 7 hours sitting or standing about, neither indulging in exercise nor showing any excitement. The venepunctures were made in a vein in the antecubital fossa with the subjects quietly seated. After the pre-meal venepuncture, each subject rapidly (within 2 to 8 minutes) "ate" the meal comprising 120 Gm. of the fat emulsified in a hand homogenizer with skim milk to make a volume of 300 ml. The carbohydrate meal consisted of about 1080 calories of boiled rice and sugar with about 200 ml. of skim milk. All of the men readily took the meals except for 2 who could not be persuaded to swallow the sardine oil emulsion.

Venepunctures were made before and at 4 and 5 hours after the meal with siliconized syringes and needles treated with Arquad,† which is a cationic agent that inhibits clotting on the surface so treated. In the few cases where a clean puncture of the vein was not achieved rapidly, a new puncture was made with a new needle. Coagulation was measured from the moment blood started to enter the syringe.

The method for determining whole blood coagulation time at 37 C. in siliconized tubes has already been described.[1] The times referred to in this paper are the averages for the 2 final tubes in the series of 4 tubes of 1 ml. of blood for each sample.

Lipemia was estimated from the optical density of the oxalated plasma as estimated in the Evelyn photoelectric colorimeter with the 620 mμ filter.

Results

The results are summarized in table 1, which gives the averages for the 5 pre-meal samples

From the Laboratory of Physiological Hygiene, University of Minnesota School of Public Health.

Supported by research grants from the National Dairy Council, Chicago, the Schweppe Foundation, Chicago, and from Mr. David Winton and Associates, Minneapolis.

* Manufactured by Durkee Famous Foods, Chicago, Ill.

† Manufactured by Armour and Co., Chicago, Ill.

TABLE 1.—*Changes in Coagulation Times (Minutes) after Various Fat and Carbohydrate Meals*

Subject	Mean pre-meal	Butterfat		Corn oil		Coconut oil		Fish oil		Carbohydrate meal	
		4 hrs.	5 hrs.	4 hrs.	5 hrs.	4 hrs.	5 hrs.	4 hrs.	5 hrs.	4 hrs.	5 hrs.
Ha	39	−7	−4	−1	−5	−6	−4	−1	−11	−2	−3
Pe	43	−9	−9	−5	−7	−8	−7	−7	−18	+1	+8
Mu	36	−8	−7	−2	−3	−7	−6	+1	+2	+5	+12
Cr	37	−5	−6	−3	−4	−7	−4	−4	−1	+2	+2
Fr	42	−8	−7	−10	−10	−10	−7	−4	+5	−5	+2
Ki	43	−6	−8	−3	−4	−5	−10	+5	+5	+6	+7
Wy	44	−11	−8	−5	−6	−6	−8	+4	0	+5	+4
Hu	43	−7	−6	−9	−9	−9	−9	−6	−1	−3	−4
Gi	39	+1	−9	−1	−2	−3	−3	−8	−3	+1	+1
Ke	49	−7	−7	−12	−5	−9	−11	0	+3	+1	+1
Gl	42	−8	−2	−4	−2	−12	−10	—	—	+6	+4
La	40	−9	−5	−6	−4	−2	−4	—	—	+2	+1
Mean	41.4	−7.0	−6.5	−5.1	−5.1	−7.0	−6.9	−2.0	−1.9	+1.9	+3.5

The differences presented are between each postmeal coagulation time (on 1 day) and the mean of all 5 premeal coagulation times for the same subject.

TABLE 2.—*Summary of Differences between Mean Clotting Times (Minutes) at Four and Five Hours after a Fat Meal and at Same Times after a Carbohydrate Meal*

	Butterfat*	Corn oil*	Coconut oil*	Fish oil†
Mean, fat meal—Carbohydrate	−9.00	−7.33	−9.21	−4.00
Variance	19.64	11.06	21.34	29.50
S.E.	±1.28	±0.96	±1.33	±1.72
t	7.03	7.64	6.92	2.33

* N = 12, t is 4.32 at $p = 0.001$ † N = 10, t is 2.23 at $p = 0.05$.

for each man and the differences between these values and those observed at 4 and at 5 hours after the meal. Shortening of the coagulation time was observed in all blood samples drawn after corn oil and coconut "oil" and in all but 1 sample after butterfat. After fish oil there was a similar tendency but the result was less uniform. After the carbohydrate meal there was, as previously observed, a tendency for the coagulation time to be prolonged.

A statistical analysis of the coagulation times is given in table 2. The effect of each fat is compared with that of the carbohydrate meal. For this purpose the values at 4 and at 5 hours after the meal for each man were averaged. It is clear that butterfat, corn oil, and coconut oil all shorten the coagulation time by some 7½ to 10 minutes as compared with the carbohydrate meal control and that the differences are highly significant. The effect of fish oil is much more variable and the average shortening is only about half as great as with the other oils. The effect of the fish oil is significant at about the 4 per cent probability level.

The various oils behave entirely differently in regard to the production of visible lipemia. The optical density data are summarized in table 3. Butterfat and corn oil uniformly produce an intense lipemia while coconut oil is remarkable in that the plasma after ingestion remains almost as clear as before. Fish oil produced intense lipemia in 2 men, moderate lipemia in 4 others, and very slight lipemia in 4 men; and these differences were not correlated with the changes in coagulation time observed in these men. Obviously, whatever may be responsible for the effects on blood coagulation is not closely correlated with the gross degree of lipemia. This confirms the previous conclusion reached from our studies on butterfat meals[1] and agrees with O'Brien's findings.[2]

These studies provoke consideration of the coagulation time as an individual characteristic. Within the accepted "normal" range of blood coagulability, do individuals tend to differ even

TABLE 3.—*Optical Density of Plasma As an Index of Lipemia*

Time	Item	Butterfat*	Corn oil*	Coconut oil*	Fish oil†	Carbohydrate meal*
Before meal	Mean	0.064	0.052	0.045	0.076	0.051
	S.E.	±0.011	±0.004	±0.002	±0.007	±0.004
Four hrs. after meal	Mean	0.385	0.410	0.080	0.236	0.049
	S.E.	±0.074	±0.098	±0.007	±0.071	±0.004
Five hrs. after meal	Mean	0.403	0.427	0.068	0.284	0.047
	S.E.	±0.067	±0.079	±0.008	±0.075	±0.003

* N = 12. † N = 10.

TABLE 4.—*Analysis of Variance in Clotting Times from Ten Subjects in Five Experiments Each Involving 1 Pre-meal and 2 Post-meal (Four and Five Hours) Values*

Condition	No. of determinations	Total variance	Per cent of total variance		
			Between individuals	Between occasions	Random
Pre-meal	50	27.53	37.34%	0.06%	62.00%
(F value)			(4.01)*	(1.10)†	
Post-meal					
(F value)	100	36.40	28.65%	33.08%	38.27%
			(8.49)‡	(9.65)‡	

* $F_{0.01} = 2.99$ † $F_{0.05} = 2.63$
‡ $F_{0.01} = 2.66$

when they are on the same diet and pursuing the same mode of life? Compared with mentally normal men, schizophrenic men may tend to be more variable from time to time in blood coagulability just as they are in some other characteristics. Further, the particular subjects in these 5 experiments are, in general, rather homogeneous in regard to their individual average coagulation times so the inter-individual variability in the group in these experiments may be an unusually small fraction of the total variability (intra- plus inter-individual variability). Accordingly, an analysis of variance with the 150 coagulation measurements on these 10 subjects should give a *low* estimate for the consistency of individual differences in respect to blood coagulability.

Table 4 summarizes the analysis of variance with the data from these 150 observations. For the pre-meal observations, 37 per cent of the total composite variance is accounted for by the differences between individuals and almost none of the variance was attributable to between-day trends. For the postmeal values, the variance from occasion to occasion is significant, of course, but even so 29 per cent of the total variance is attributable to consistent differences between individuals. In other words, in this series the different individuals show consistent individual differences in spite of the fact they were all subsisting on exactly the same diets and were maintaining the same mode of life in general. Finally, the analysis of variance shows, as we would expect, that there was no significant difference between days for the pre-meal measurements. For the postmeal values, variance due to differences between occasions is highly significant statistically.

DISCUSSION

Most of the previous studies on blood coagulation after fat meals have involved butterfat, either as the only fat or as a major constituent in a fatty meal. As we have pointed out,[1] the evidence, independent from our own, is overwhelmingly in agreement that butterfat does indeed increase the coagulability of the blood. The data in the literature on the effects of other food fats are very few. Duncan and Waldron[3] reported shortening after meals of olive oil and of corn oil as well as of butterfat and later[4] they provided data indicating that corn oil and butterfat were essentially the same in their effects. Finally, on the basis of experiments with oleomargarine and a single trial of a hydrogenated fat (Crisco) the same workers concluded that "apparently the more saturated the fat, the less effect it has on coagulation."[5]

Our results do not agree with this last conclusion; if anything they indicate that all

food fats tend to shorten the coagulation time but that the more saturated the fatty acids in the fat, the greater is the effect. The least saturated oil we used, sardine oil, had less effect than the others and there was a slight trend for the effects of the other fats to decrease in the order of decreasing saturation. However, the differences between corn oil, butterfat, and coconut oil are statistically not significant in spite of the great range in saturation they represent.

After re-analysis of the data of Waldron and Duncan[4, 5] we believe their suggested conclusion about the effect of fatty acid saturation is not supported by their own data. Firstly, in most cases they used different patients to test the different fats and no serious emphasis can be given to differences in the coagulation response in such group comparisons. More particularly, we note that in all of their studies corn oil and butterfat were not significantly different, though corn oil is one of the least and butterfat one of the most saturated of the common food fats. Their single result on 1 patient fed hydrogenated shortening is not significant, of course. Only in the experiments with oleomargarine is there a significant difference between fats in the experiments of Waldron and Duncan. But we have no information about the fatty acid composition of the oleomargarine they used and it is idle to speculate about its degree of saturation. Oleomargarine is by no means a uniform substance, and different oleomargarines, or even the same brand bought at different times, have widely variable compositions and degrees of hydrogenation.

The duration and time of maximum effect of the fatty meal is of interest. Waldron and Duncan[5] reported a maximum shortening of clotting time 1 hour after the fatty meal, with considerably smaller changes at 2 and at 3 hours. However, we found only a small effect at 1 hour and the maximum effect was in the period from 4 to 6 hours after a fat meal rather than at 2 hours or at 6 hours. Presumably, technical differences in the methods used account for the variable appearance of the time of greatest coagulability.

In any case, the effect on coagulation seems to be limited to a few hours after a fatty meal. We have not demonstrated the total duration of a significant effect but it is less than 15 hours and does not appear to be cumulative from day to day.

Evidence for the latter statement was obtained in studies on 2 groups of men who were studied on low- and high-fat diets. Fourteen schizophrenic men, different individuals but like those studied with the special fat meal reported above, were maintained on a diet high in ordinary mixed food fats (40 per cent of calories from fats) and then were changed to a low-fat diet (12 per cent of calories from fats) that provided the same amount of calories, proteins and vitamins. After 2 weeks on the low-fat diet the average before-breakfast coagulation time was 41.36 minutes as compared with an average of 40.23 minutes for the before-breakfast value on the high-fat diet. This small difference is statistically not significant and an equally insignificant difference, in the opposite direction, was obtained with 14 obese university students who were controlled on 2 reducing diets of constant calories but differing in fat content (20 per cent and 60 per cent fat calories). Half of the students had the high-fat diet for several weeks and then changed to the low-fat diet while the other students made the reverse order of change. The average before-breakfast coagulation time was 49.07 minutes on the high-fat diet and 46.64 minutes on the low-fat diet.

It is not clear what stage (or stages) in the events in coagulation is altered after a fat meal. The experiments of O'Brien[2] indicate that the effect on coagulability of a fatty meal is prevented by platelet action. We found a reduction in the prothrombin time but this effect was smaller and less significant than the effect on the whole blood coagulation time.[1] Salvini and Sordi[6] observed a small increase in prothrombin activity as well as a shortening of the coagulation time of recalcified plasma but their most striking result was a marked decrease, averaging 40 per cent, in the "heparinoid substances" as estimated by the method of Gibson and co-workers.[7] Fullerton, Davie, and Anastosopoulis[8] observed shortening of the coagulation time of recalcified plasma in the presence of snake venom. Finally, it has

been claimed[4] that the effect of the fat meal is inhibited to some extent by the simultaneous ingestion of sugar.

Summary

Twelve men were studied on 5 occasions before and at 4 and 5 hours after isocaloric meals of butterfat, corn oil, coconut oil, and sardine oil, emulsified with skim milk, and of boiled rice and sugar with a similar amount of skim milk.

After the carbohydrate meal the average coagulation time of whole blood in siliconized tubes was slightly lengthened, but all of the fatty meals produced a significant shortening of the coagulation time. Compared with after the carbohydrate meal, the average coagulation times were 4 minutes shorter after the fish oil and from 7.3 to 9.2 minutes shorter after the other fat meals.

Visible lipemia was marked after butterfat and corn oil, almost nil after coconut oil, and variable from individual to individual after the fish oil. There was no correlation between visible lipemia and the coagulation time.

The effect of the fatty meal seems to be limited to a few hours after the meal and is not cumulative. Measurements of before-breakfast coagulation time on 2 groups of men on controlled low-fat and high-fat diets disclosed no effects of the different character of the diets eaten during the preceding days.

An analysis of inter- and intraindividual variability showed that coagulation time tends to be an individual characteristic, even when all of the individuals are well within the extremes of accepted "normality," but that a fat meal tends to change the bloods of all individuals in the same direction.

Acknowledgment

Dr. F. W. Sheeley, Superintendent of the Hastings State Hospital, made it possible to do the work at his hospital. We are grateful to Mrs. Helen Williams, to Mrs. Rose Marie Keidel, to Dr. B. Bronte-Stewart, and to Dr. Josef Brozek for help in one or another aspect of the work. The faithful assistance of the young men volunteer aides from the Church of the Brethren is especially appreciated.

Summario in Interlingua

Dece-duo homines esseva studiate a 5 occasiones ante e 4 e 5 horas post isocaloric repastos de grassia butyric, oleo de mais, oleo de coco, oleo de sardina—omne istos emulsificate con lacte discremate—e ris bullite e sucro con un simile quantitate de leacte discremate.

Post le repasto a hydratos de carbon, le tempore medie de coagulation de sanguine integre in tubos revestite de silicium esseva levemente prolongate, sed omne le repastos grasse produceva un significative reduction del tempore de coagulation. In comparation con le valores obtenite post le repasto a hydratos de carbon, le tempore medie de coagulation post le repasto a oleo de pisce esseva 4 minutas plus breve; post le altere grassias, illo esseva 7,3 e 9,2 minutas plus breve.

Lipemia visible esseva marcate post grassia butyric e oleo de mais; illo esseva quasi absente post oleo de coco; e illo variava ab un individuo al altere post grassia de pisce. Nulle correlation existeva inter le lipemia visibile e le tempore de coagulation.

Le effecto del repasto grasse es apparentemente limitate a alicun horas post le repasto individual; illo non es cumulative. Mesurationes del tempore de coagulation ante le prime repasto del die esseva executate in 2 gruppos de homines mantenite super dietas a basse e a alte contento de grassia, respectivemente. Le resultatos reflecteva nulle effectos correlationate con le differente dietas ingerite durante le dies precedente.

Un analyse del variabilitates inter- e intraindividual monstrava que le tempore de coagulation tende a constituer un characteristica individual, mesmo quando omne le individuos se trova intra le limites del extremos de lo que es acceptate como "normal," sed que un repasto grasse tende a alterar le sanguine de omne individuos in le mesme direction.

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Although rheumatic heart disease, coronary atherosclerosis, and hypertension are the most frequent causes, thyrotoxicosis, constrictive pericarditis, pulmonary embolism, malignant disease in the mediastinum, accidental electric shock, and digitalis administration are other causes. The last factor was referred to by Mackenzie in 1911. Benign "idiopathic" atrial fibrillation is not uncommon in healthy adults with excesses of work, tobacco, and emotion.

Of 500 consecutive cases, 30 per cent had rheumatic heart disease. Relative advantages of atrial fibrillation include (1) ease of control of ventricular rate, (2) decreased incidence of subacute bacterial endocarditis, (3) freedom from paroxysmal attacks. A clot was found in the left atrium of 43 of 106 patients (40 per cent) with atrial fibrillation and 3 of 144 patients (2 per cent) with sinus rhythm.

Of 32 patients with systemic embolism preoperatively, 22 had atrial clot at operation and 5 of these 22 suffered operative embolism. "So far not one of the 32 patients with a past history of systemic embolism has experienced further embolism in the years following operation."

The authors introduce their article with the following well-turned phrases of Hay and Jones: "The auricles pipe and the ventricles must dance . . . a dance that sometimes leads to death."

McKUSICK

Experimental Response of the Human Body to a Known Periodic Force as a Measure of Ballistocardiographic Fidelity

By G. P. Wilson, M.S., D. M. Cunningham, M.S., and H. E. Griswold Jr., M.D.

The vibrational characteristics of the body and the support on which it rests were investigated by the direct approach of shaking it and measuring its motion and the motion of the support. Both a very stiff and a very weak, light support were used. Close correlation was obtained between body displacement and light support displacement; body motion greatly exceeded that of the stiff support. Single mass resonant frequency was set by the dorsal skin stiffness when the support was very stiff and by the support stiffness when the light support was used. With both supports the body exhibited multi-mass motion in the frequency range above 6 c.p.s.

WHEN periodic or transient motions of any object are to be analyzed for the purpose of determining the excitation forces, it is essential that the response of the object to a well-defined forcing function be known. If the moving object is a simple system having up to 3 rigid concentrated masses and 3 weightless springs and the damping forces acting on the masses are known, the theoretic solution for the relation between a periodic forcing function and the displacements of the 3 masses is indicated in standard textbooks on vibration. For less ideal systems (i.e., a system where mass and spring characteristics are inseparable) qualified theoretic approaches have been used to shed some light on the responses of the dynamic system. However, a dynamic system as complex as the human body defies analysis from any of the classic viewpoints. The human body is composed of members and organs that vary as to mass, specific gravity, and compliance. Indeed, it does not seem possible to anticipate the forces acting on the body when the motion of some point is known or the motion of a platform on which the body rests is known. Reversing the problem would seem equally difficult.

More specifically, information is needed on what portion of the ballistocardiographic record is due to circulatory forces alone as against the contribution of inertial loading caused by the various loosely connected parts of the body and the supporting table. There is very little doubt that all the waves on the record are produced by the motion of the heart and the blood it contains throughout the cardiac cycle, movement of the blood into and out of the heart, and circulation of blood through the major arteries. However, these heart and blood motions will not be matched by body motion (each motion being inversely proportional to mass) because all parts of the body do not move in phase.

The response (movement) of any spring-mass-damping system to a transient force can be predicted if the response of this system (the body) is known when a sinusoidal forcing function is applied step by step for all of the frequencies involved. This is true because any transient force can be synthesized from its frequency components.

Choosing the site for application of a sinusoidal force to the body presents a problem. Even if the heart could be shaken directly, this would not entirely represent what would happen when the cardiovascular force was generated by blood moving around the arch of the aorta. However, when the over-all vibrational characteristics of the body are required, the actual location of the applied force is of minor importance as long as the magnitude of the applied force is known. The center of mass of the body is affected similarly no matter where the force is applied. Newton's second law, $F = ma$, applies, whether or not the mass is rigid, if we specify that the acceleration, a, be that of the center of mass of the body at any

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Aided by the Maybelle M. Dant Heart Research Fund and PHS Heart Research Grant, H-2151.

instant, regardless of the momentary configuration of the body. Much attention is currently being given to the empirical analysis of ballistocardiographic records, but very little attention has been given to the dynamic response of the body.

Because of inconsistencies in data taken on both a very stiff ballistocardiograph table and on a weak swing-type ballistocardiograph, attention was centered on the measurement of body displacement when a known forcing function was applied.

The purpose of the present investigation was to measure the movement of the center of gravity of the human body, when a known sinusoidal forcing function of constant amplitude and varying frequency was applied to the ankles and to analyze the results in the light of existing vibration theory. The effect of a large change in stiffness of the supporting table was also to be evaluated.

Method

The subject lay on his back on either a rigid 80-pound table with stiff supports (fig. 1), or on an 11-pound camp cot supported by 4 wires to form a bifilar pendulum (fig. 2). The unloaded natural frequency of the stiff table was 35 c.p.s. and that of the pendulum 0.3 c.p.s. The natural frequency of the stiff table when loaded was between 25 to 28 c.p.s. but the natural frequency of the pendulum does not vary with load. No external damping was applied in either system. Measurements were confined to the head-foot direction in every case. A loud speaker voice coil was securely strapped to the ankles of the subject and inserted into the field of the permanent magnet of the speaker. The weight of the voice coil assembly was about 8 ounces. The effective spring constant of the ankle connection was about 50 pounds per inch. The permanent magnet of the speaker was mounted very securely on the concrete floor. In a smaller number of control tests the voice coil was attached to the head of the subject. Sufficient electric power was supplied to the coil to produce a sinusoidal force output of about 2.0 pounds. This output was maintained constant by monitoring the voltage to the voice coil over a frequency range of from 1 c.p.s. to 20 c.p.s. at increments of ½ c.p.s. Displacement measurements were made with 2 8-ounce linear differential transformers; 1 was strapped tightly over the ischial tuberosity of the subject and to the side of the support in the case of the swing. In the case of the stiff table, a Statham resistance transducer at the elastic center measured the table displacement. Voice coil input voltage and

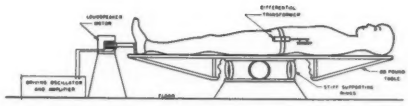

Fig. 1. High-frequency table and shaker.

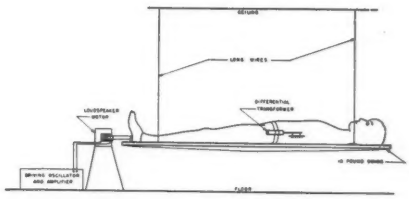

Fig. 2. Low-frequency swing and shaker.

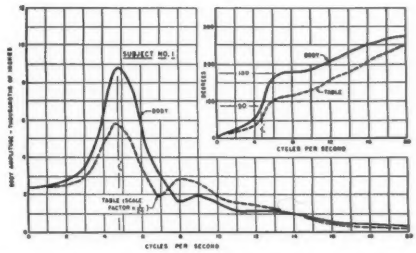

Fig. 3. Amplitude and phase lag of body and table for an exciting force F_0 of constant amplitude (F_0 = 2 lb.).

the 2 displacements were recorded on a Sanborn model-67 4-channel recorder. Measurements of amplitude were made at a point of the record where the ballistocardiograph created the least interference. Each datum represented a steady state of vibration.

Results are presented for 1 typical nonobese subject on the heavy high-frequency table and on the light low-frequency pendulum. She was 5 feet 7 inches tall, weighed 135 pounds, and had a resonant frequency on concrete of 4.4 c.p.s. On the high-frequency table a typical body-amplitude curve, figure 3, started at the 0 frequency or static value, increased to the peak corresponding to the natural frequency of the body on the skin, f'_n, at 4.8 c.p.s., and then dropped off to a low-amplitude value at 20 c.p.s. with 2 or more minor resonances in the latter range. Amplitude curves for the table itself had approximately the same shape as the body-amplitude curves, but the actual values were only $\frac{1}{44}$ as high. Cross-strapping and head-foot compression of the body to the table resulted in a small improvement of this ratio.

When the body was excited on the light low-frequency swing, the coupling forces between body and swing were much higher than the restoring forces on the pendulum, so that there was only a

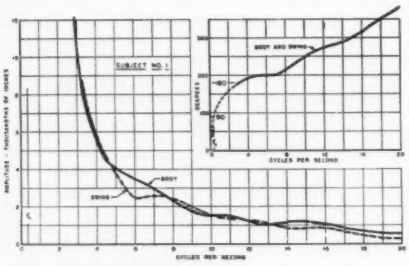

FIG. 4. Amplitude and phase lag of body and swing for an exciting force F_0 of constant amplitude (F_0 = 2 lb.).

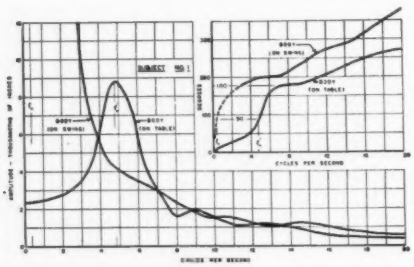

FIG. 5. Comparison of body amplitude and phase lag on table and swing.

small amount of relative motion between body and swing, but the combined system had a large amplitude of motion. Resonance occurred at a lower frequency, f_s, on the swing support (figs. 4, 5), but the remainder of the amplitude-frequency curve above resonance was not greatly different from that of the high-frequency table (fig. 5), except that secondary resonances were less pronounced for the swing.

The phase lag of body amplitude behind forcing function followed the same pattern for both types of supports. Starting at 0 angle of lag for 0 frequency the lag increased to 90° at resonance; then it increased further to 180° at about twice the resonant frequency where the relationship leveled off momentarily before continuing up to 270° or 400° at 20 c.p.s.

A theoretic amplitude-frequency curve for an ideal single-mass body and high-frequency table system would have only 1 resonant peak at 4.8 c.p.s. and would drop off smoothly above resonance. The decrease in amplitude above resonance would be more rapid than that for the experimental curve.

No results are presented for the cases where the head was excited instead of the feet, as the procedure was difficult and the result erratic, although the nominal shape of the frequency curves was the same. Difficulties in attaching the voice coil solidly to the head and rocking of the head on the support caused artifacts in the records.

DISCUSSION

The fundamental difference between amplitude curves obtained for subjects on low-frequency and high-frequency supports is that the "skin spring" governs the motion of the body when a stiff support is used and the supporting "spring" governs the amplitude when a weak support is used, and the support is light compared to the body. This phenomenon was discussed in detail by Talbot and Harrison.[1] The "skin-spring" resonance occurs in the middle of the ballistocardiographic spectrum, while our swing resonance is below it.

In addition to verifying the above conclusions, our research shows that there are several other resonant points above skin or support resonance. Also, there is a flattening, a slower decay than theory indicates, of the curves at frequencies well above resonance, especially when the low-frequency support is used. The secondary resonances and the flattening of the amplitude curves above resonance indicate that the body does not move as a unit. The various loosely connected organs of the body move together only at frequencies up to, and possibly slightly exceeding, the resonant frequency of the whole body on the dorsal skin. The assumption made is that the body-skin-resonant frequency is probably the lowest resonant frequency of any organ (mass)-compliance (spring) combination. As frequencies above body-skin resonances are reached, the individual organ resonances begin. However, these single-organ resonances are much less pronounced on the low-frequency swing. This may be due to the fact that there is a restoring force at every point of contact for the stiff support systems. The number of secondary resonances observed varies from 1 to 4. The number increases with obesity of subject and stiffness of support. At high frequencies fatty regions of the body apparently do not move with the muscular and skeletal parts, nor do the fatty regions move together as a unit. Obviously the organs in the thoracic area cannot move as a unit at high frequency because of variations in density and compliance.

No attempt is made at this time to associate any particular secondary peaks with the

resonance of a certain part of the body. A very important question must be answered first: What does the displacement pickup at the hip measure? If the displacement measured represents the true motion of the skeletal part of the pelvis, how does this compare with the motion of the center of gravity of the whole body at any instant? Even if the hip displacements corresponded identically with the pelvis, how does this compare with the motion of the center of gravity of the whole body at any instant? Even if the hip displacements corresponded identically with the displacement of the whole skeleton, and some investigators doubt this, it would not correspond to the movement of each organ or it would represent the average motion of all the parts. A paradoxical situation exists: If the displacement transducer were firmly attached to the static center of gravity of the body, it would still fail to record the movement of the center of gravity (movement of the parts summed up) under dynamic conditions.

A somewhat simplified analogy will help in the understanding of the problem. Consider an ordinary coil spring hanging from the ceiling and excited vertically at its lower end by a sinusoidal cam. As the cam is turned very slowly every point on the spring moves with a displacement inversely proportional to its distance from the cam. The center of gravity of the spring, the midpoint in this case, moves with just one half the amplitude of the cam. All points on the spring move together or are said to be in phase. As the speed of the cam is increased, a frequency will be reached where a fully developed wave motion will be apparent and all points of the spring will move out of phase. There will still be a definite relation between the force on the end of the cam and the motion of the dynamic center of gravity, but the dynamic center of gravity will not correspond to the static center of gravity (the midpoint of the spring).

The frequency-response curve for subject no. 1 on the low-frequency swing (fig. 4) indicates purely wave motion in the body, or a large number of very small masses moving out of phase with each other, in the region above 16 c.p.s. Acoustic theory indicates that in a continuous elastic highly damped medium the amplitude of a given point will not change with frequency for a constant amplitude force excitation, but the phase shift between the displacement of a given point and the forcing function will increase linearly with frequency. Phase lag of body behind exciting force is very nearly linear with frequency above 16 c.p.s. (fig. 4).

The problem of measuring the exact motion of the dynamic center of gravity of the human body may never be solved with a high degree of accuracy, but it may be possible, however, to improve on present instrumentation. A point in the body may be found that more nearly follows the motion of the center of gravity, or a method may be found for restraining the body in such a way that it moves more like a single mass. One would expect the light support to approach the motion of the center of gravity of the body by integrating the movements of the various parts. Figure 4, however, indicates that the support transducer does not approach the motion of the center of gravity any better than the hip transducer.

When a known forcing function of any significant frequency can be applied to the human body and an acceleration can be measured that, at any instant, is universely proportional to the mass of the body, then the art of ballistocardiography will have advanced to the point where the forces giving the blood its gross acceleration can be predicted. When these forces have been predicted accurately, the problem of determining the exact pattern of blood flow still remains.

Summary

The frequency-response curve for the human body is dominated by the dorsal skin spring when the support has a high natural frequency. The body on the stiff table moves approximately as a single-mass system up to about 6 c.p.s. above which many secondary resonances occur. The response curve for the body on the pendulum swing is governed by the vibrational characteristics of the pendulum when the pendulum natural frequency is only a fraction of that of the body on the skin. The body and

swing move almost together if the mass of the swing is say less than $\frac{1}{15}$ that of the body. Whatever damping is in effect in the stiff-table system is produced by the skin and has a value of about 1.15 critical.

Records taken with the exciting force on the head instead of the feet indicate the same general response but the head tended to rock and the results were more erratic.

Less secondary resonance occurs on the light pendulum swing because only very small external restraints are acting on the body. On the stiff table there is a restoring force at every point of support that tends to increase the number of secondary resonances.

The phase shift curves also verify that either system behaves as a single-mass system up to about 6 c.p.s. Above this frequency various parts of the body do not move together.

An almost pure wave-type motion exists in the body above 16 c.p.s. when the weak support is used.

If the transducer measures the true motion of the "dynamic" center of gravity of the body, it does not matter whether or not the body moves as a rigid unit. If the support is light enough and the restoring forces on the support are small enough, the true motion of the "dynamic" center of gravity is the true ballistocardiograph.

Summario in Interlingua

Le curva de frequentia/responsa pro le corpore human es dominate per le resorto dorsal del pelle quando le supporto possede un alte frequentia natural. Le corpore super le tabula rigide se move approximativemente como un systema a massa unic si le frequentia es infra circa 6 cps. Supra iste valor multe resonantias secundari se manifesta. Le curva de responsas pro le corpore super le balancia pendulate es governate per le characteristicas vibrational del pendulo si le frequentia natural del pendulo es solmente un fraction del frequentia del corpore super le pelle. Le corpore e le balancia se move quasi insimul si le massa del balancia es minus que approximativemente un dece-quinto del massa del corpore. Effectos de amortimento que occurre in le systema a tabula rigide es producite per le pelle e amonta a circa 1,15 del valor critic.

Registrationes obtenite per applicar le fortia excitatori al capite in loco de al pedes indica le mesme responsa general, sed le capite tendeva a bascular, e le resultatos esseva plus erratic.

Minus forte resonantias secundari occurre con le leve balancia pendulate, proque in iste caso solmente minor fortias restrictori exerce un action super le corpore. Super le tabula rigide, un fortia restauratori es active in omne puncto de supporto e tende a augmentar le numero del resonantias secundari.

Le curvas de alteration phasic etiam demonstra que ambe systemas se comporta como systemas a massa unic si le frequentias es infra circa 6 cps. Supra iste frequentia, varie partes del corpore non se move insimul.

Un motion de typo quasi purmente undate existe in le corpore supra 16 cps si le supporto de fortia minor es usate.

Si le transductor mesura le ver motion del "dynamic" centro de gravitate del corpore, il non importa si o non le corpore se move como un unitate rigide. Si le supporto es satis leve e si le fortias restauratori super le supporto es satis parve, le ver motion del "dynamic" centro de gravitate es le ver ballistocardiographo.

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CLINICAL PROGRESS

The Artificial Kidney—Past, Present, and Future

By W. J. KOLFF, M.D.

THE name *artificial kidney* was first suggested by Abel, Rowntree, and Turner,[1] and indicates perfectly the intended function of the apparatus. All currently used artificial kidneys remove retention products from the blood, by exchange through a semipermeable membrane.

TYPES OF ARTIFICIAL KIDNEYS

Blood Pumped Through Cylindrical Tubing. The dialyzer designed by Abel, Rowntree, and Turner utilized cylindrical collodion tubing through which the blood flowed while the rinsing fluid circulated outside. The same principle of design but with cellulose tubing was followed by Haas,[1] and by Murray, Delorme, and Thomas.[1] One of the disadvantages of these kidneys was the large volume of blood required to fill them as compared to the relatively small dialyzing area. The Murray artificial kidney has a blood volume of 560 ml. and a dialyzing surface of 0.88 M.^{2}, which is not too unfavorable because the tubing is small (¼-inch diameter), but unfortunately it is too thick-walled for adequate dialysis. With thin-walled cellulose tubing the size of a drinking straw, the prospects for good dialysis are better. Rosenak[2] has induced the American Viscose Company to make such tubing and he uses it in a counterflow arrangement with 2 concentric tubings. Blood runs through the inner cellulose tubing while rinsing fluid runs in the opposite direction through the outer tubing.

The rotating type of artificial kidney combines a large dialyzing area (2.4 M.^{2}) with a small volume of blood (600 ml.). A thin film of blood is propelled by gravity through cellulose tubing wrapped around a slowly rotating drum. There is dialysis through the tubing but filtration does not occur because there is hardly any difference in hydrostatic pressures across the membrane. The rotating type of kidney was described in 1943 by Kolff and Berk, and detailed plans were published in 1946 and in 1947.[3] To encourage their clinical use, 4 kidneys were made in Holland during World War II and subsequently were donated to several medical centers. One was sent to London, one to Montreal, one to New York, and the fourth one disappeared behind the iron curtain. Kidneys of this type have also been made by Allis-Chalmers* and, with modifications, by the Peter Bent Brigham Hospital group,[4] by Olsen.†

The reverse of the usual system of dialysis is used by Guarino and Guarino[5]: blood is outside the cellulose tubing and rinsing fluid is inside. This design in its present state of development, although very interesting, has a low clearance and no safeguard against air embolism or against overhydration of the patient if a leak should develop in the cellulose tubing.

To provide a limited space for blood but a large dialyzing area one can enclose the cellulose tubing or sheets between ridges or screens. As the blood is forced through the narrow space there is a hydrostatic pressure difference across the membrane and ultrafiltration as well as dialysis takes place. The most effective of this type currently used was designed by Skeggs, Leonards, and Heisler,[6] who sandwiched sheets of cellophane between grooved rubber plates. Its assembly requires adequate training.

As early as 1923, Necheles[1] designed a type

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Aided by grants from The Cleveland Area Heart Society.

Modified from a presentation at the meeting of the American Society for Artificial Internal Organs, at Atlantic City, New Jersey, June 5, 1955.

* Allis-Chalmers Manufacturing Company, Milwaukee, Wis.

† Edward A. Olsen, Main St., Ashland, Massachusetts.

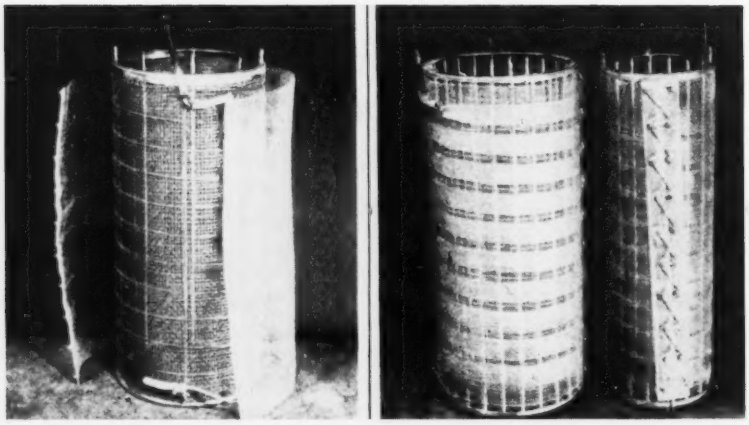

FIG. 1. Cellulose tubing between 2 screens.[7]

of dialyzer in which "Goldschelegerhaut" (peritoneum) was compressed between screens. Alwall,[7] in Sweden, used cellulose tubing wrapped around a screen and surrounded in turn by a second screen that was fitted very much the way a corset is fitted around a body (fig. 1). Why he changed from this to a system of stainless steel ridges,[1] which must be expensive and difficult to make, is not altogether clear.

Von Garrelts[8] made a stationary coil in which cellulose tubing and wire mesh are wound together, thus the volume of blood in the cellulose tubing is small, the dialyzing area is large, and the unit is compact (fig. 2).*

Inouye and Engelberg[9] ingeniously used cheap, disposable plastic screen in a stationary coil that they fitted into a pressure cooker (fig. 3). Kolff and Watschinger[10, 11] have further developed this type of artificial kidney and have put it into a tin can, making a dialyzing unit that is cheap, disposable, and can be mass-produced (fig. 4).

Resin Artificial Kidneys. Some work has been done with resin artificial kidneys. That resins absorb, or rather exchange, certain ions is well known. Muirhead and Reid[1] showed in animal experiments that certain resins also absorb urea. Di Marchi and Brönniman,[1] in Switzerland, and Bonanome,[12] in Italy, have used resin artificial kidneys in treating patients. The field has not been developed yet, but Zinsser[13] has demonstrated the potentialities of resins in absorbing various retention products. Resins now are available in sheets.

The ideal artificial kidney has not yet been built; usually a compromise is necessary to arrive at a usable unit, and one or more desirable qualities must be sacrificed. A good artificial kidney should have a large dialyzing area for adequate clearance, and continuous movement both of blood and of rinsing fluid. It must operate with a small volume of blood and maintain a constant volume of blood in the machine —causing no change in blood volume in the patient. It must have good visibility so that if a leak occurs in the dialyzing membrane it will be seen immediately. It must have controlled temperature of rinsing fluid. The rinsing fluid must be of the correct composition (10 per cent CO_2 in O_2 bubbled through it to maintain the pH at 7.4). The blood must not come in contact with glass or metal or materials that promote clotting and require the use of large doses of heparin. The dialyzing unit must be easy to assemble and to clean; it may be prefabricated and disposable. It must be sterilizable (preferably after assembling). The apparatus should be easy to operate.

If there is a pressure gradient across the dialyzing membrane it is preferable that the

* It has been brought to my attention that S. S. Rosenak, G. D. Oppenheimer, and A. Saltzman exhibited a small stationary coil kidney at the Annual Meeting of the American Urological Society in Boston 1948, which may have been the first of this kind in this country.

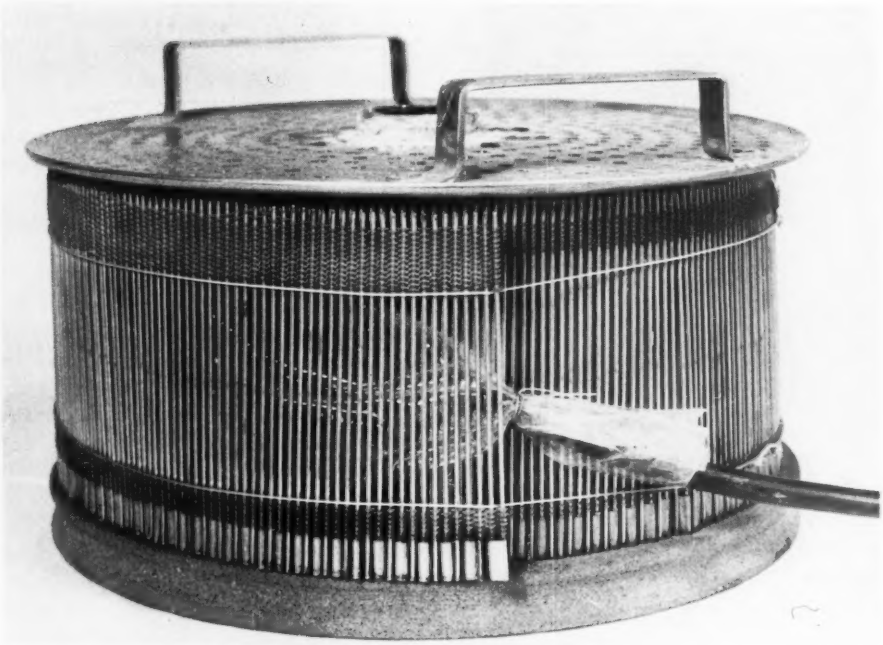

FIG. 2. Stationary coil of cellulose tubing and wire mesh.[8]

FIG. 3. Cheap plastic screen in a pressure cooker.[9]

pressure on the blood side be higher than that on the rinsing fluid side. The reasons are (1) in case of a leak, blood coming into the rinsing fluid can be seen, whereas rinsing fluid going into the blood is difficult to detect (infusion of rinsing fluid into the blood may lead to over-hydration of the patient, and as the rinsing fluid is not sterile it may introduce bacteria) and (2) positive pressure on the blood side will cause some ultrafiltration, thus counteracting the colloid osmotic forces of the blood plasma that operate in the opposite direction.

FIG. 4. Disposable, mass-produced unit.[10, 11]

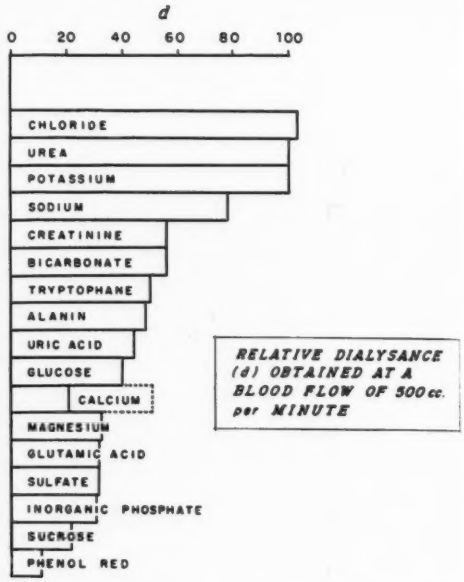

FIG. 5. Urea clearance of 100; phenol clearance of only 3.[14]

The following considerations deserve attention: sedimentation in the apparatus and minimum clearance. When the blood flow is small, sedimentation of erythrocytes may take place in the apparatus, so that only plasma comes out. The settling out of red cells may occur in multiple-channeled dialyzers with parallel and consequently slow flow in each channel. It also occurs when dialysis is interrupted for a time.[1]

There is a minimum clearance necessary for an artificial kidney to be clinically useful. It is a frustrating experience to remove 30 Gm. of urea during a day's dialysis only to discover on the next day that the patient's blood urea is the same as it was prior to dialysis: a gain of 1 day only has been obtained; whereas, with more efficient dialyzers 4 or 5 days may be gained.

If we express the efficiency of an artificial kidney in dialysance or clearance, we usually express it in *urea* dialysance or clearance. Wolf and co-workers[14] have shown that the urea level provides the most favorable index of clearance (fig. 5). For example, with a urea clearance of 100, the clearance for phenol red is only 3. Artificial kidneys with clearances of 120 to 180 ml./min. are now available, and contraindicate use of less effective devices that require more time, longer supervision, longer heparinization, and offer greater hazard of hemorrhage.

Membranes with Greater Porosity. The possibilities of developing kidneys with membranes of greater porosity have hardly been explored. The rate of urea clearance probably would not be increased, inasmuch as the diffusibility of urea through the fluid layer coating the membrane, rather than the number or size of the pores of the membrane seems to be the limiting factor. The pore size in our present cellulose tubing is 25 angstrom units. By treating the tubing with zinc chloride solutions the pore size may be increased to 170 Å.[15] Hemoglobin will pass through at 60 Å. By using membranes having greater porosity another category of products might be removed from the blood by dialysis. Unfortunately, treatment of membranes with zinc chloride seems to make them more brittle.

Damage to Blood and Unfavorable Reactions

Pyrogenic Reactions from Cellulose. Visking tubing is made from cotton linters. It is not a pure substance such as cellulose acetate, cellulose acetate butyrate, or ethyl cellulose, but is regenerated cellulose. According to the Visking Corporation, it contains glycerin, water, and 0.1 per cent sulfur. The inside of the roll of cellulose as it comes from the factory is sterile (although the factory does not guarantee this). If properly stored, it is unlikely that microorganisms will attack the tubing. Cellophane sheets and cellulose tubing have been considered as requiring chemical treatment or extensive boiling to preclude pyrogenic reactions in the patient. I have no personal experience with unboiled cellophane sheets, but am convinced that boiling of cellulose tubing is unnecessary. We have not boiled our tubing in the last 40 consecutive dialyses and we have had not a single pyrogenic reaction. With prolonged boiling or soaking the cellulose seems to lose some of its shininess and smoothness; the rough surface may injure the blood corpuscles.

Leukopenia and Thrombocytopenia. De Leeuw and Blaustein[1] made microscopic studies of blood passed through the rotating type of artificial kidney, and observed that the cellulose tubing was coated with leukocytes. This explains the transient leukopenia observed during vividialysis. Transient thrombocytopenia may be similarly produced. De Leeuw and Blaustein's experiments were performed with cellulose tubing that was boiled. Whether the unboiled cellulose attracts the leukocytes equally is not known. In the construction of artificial lungs, although polyethylene and cellulose are equally permeable for oxygen and carbon dioxide, polyethylene is preferred, since it is less likely to induce adherence of leukocytes and thrombocytes.

Hemolysis. With the rotating type of artificial kidney, hemolysis cannot always be avoided, but it is less often encountered with unboiled cellulose. Some patients with uremia have very fragile cells, and hemolytic anemia occurs without using the artificial kidney. Hemolysis should be avoided if it is at all possible, but there is no proof that it further impairs renal function in kidneys already severely damaged.

Change in Blood Pressure. Falls in blood pressure may be due to changes in blood volume or to substances comparable with the pyrogens. In the author's experience falls in blood pressure are rare.

When the blood flow through the apparatus is 200 ml./min. or more, *a rise in blood pressure* frequently is observed; with lower flow rates it is unusual. This rise in blood pressure probably occurs with all types of artificial kidney. Usually the blood pressure returns to its previous level during the night after treatment. In patients in whom electrolyte disturbance can be ruled out, it seems most likely that some pressor substance has been formed in the blood during handling outside the body. Serotonin may be the substance. Page and McCubbin[16] showed that serotonin infused in patients with hypertension is pressor.

Hemorrhage. The use of siliconized glass and plastic tubing has greatly reduced the need for heparin;[1] consequently, the danger of hemorrhage usually is negligible. The problem still exists, however, in some patients who are referred to the artificial kidney as a last resort. A nasal hemorrhage or the trickle of blood from a fresh tracheotomy, running down the trachea, may be a fatal complication. At the end of dialysis, protamine sulfate (1 mg. for each mg. of heparin used) may immediately return the clotting time to normal. It should be given very slowly.

Experimental work is needed to learn how to eliminate the dangers of heparin. Several possibilities may lead to this goal. For example, heparin might be continuously administered through an automatic syringe on the arterial side, with protamine sulfate simultaneously being administered in the outflow end of the artificial kidney. Heparin might be removed by an anionic resin. Since heparin consists of a high percentage of ester sulfate, its affinity for certain resins might be greater than that of any other substance in the blood. The use of sodium citrate to bind calcium in the blood has been suggested as a means to prevent clotting, but

TABLE 1.—*Composition of Rinsing Fluid for Artificial Coil Kidney*[10]

Component	Gm./100 L.	mEq./L.					
		Na^+	K^+	Ca^{++}	Mg^{++}	Cl^-	HCO_3^-
NaCl	570	97	—	—	—	97	—
$NaHCO_3$	300	36	—	—	—	—	36
KCl	40	—	5	—	—	5	—
$CaCl_2$	28	—	—	5	—	5	—
$MgCl_2$	15	—	—	—	3	3	—
Total		133	5	5	3	110	36

Invert sugar (Travert) 0.4 per cent.
Lactic acid to adjust pH to 7.4.

no practical way has yet been found. A calcium-binding resin might bind the calcium ion in the blood, as described by Clark, Gollan, and Smith.[17] It might be used at the entrance to the artificial kidney. Calcium can be restored to the patient easily through another vein.

Postdialytic Oliguria. In patients with chronic uremia, urinary output may diminish on the day of, and on the day after, treatment with the artificial kidney. Merrill, Legrain, and Hoigne[1] added urea to the rinsing fluid to maintain the blood urea while removing retention products other than urea. They observed no reduction in volume of urine and concluded that diminished diuresis is due to reduction of blood urea levels. This may not be the only explanation, since diuresis usually is restored before the blood urea has returned to its former level.

Overloading with Sodium from the Rinsing Fluid. The electrolyte content of the patient's blood plasma should not be restored to normal in the course of a single dialysis. Overloading with fluid and electrolytes of bilaterally nephrectomized dogs resulted in their developing a malignant type of hypertension,[18] and a similar course is conceivable and must be carefully avoided in the virtually renoprival patient. Table 1 gives a suitable composition for the rinsing fluid.

INDICATIONS FOR TREATMENT WITH THE ARTIFICIAL KIDNEY

Acute Anuric Uremia

Treatment with the artificial kidney may be indicated during acute uremia due to any one of the following conditions.[19]

1. *Acute Tubular Necrosis* (erroneously called "lower nephron nephrosis"), also called "acute tubular degeneration," "necrotizing nephrosis," and, in its most severe expression, "symmetrical cortical necrosis." Conditions favoring the occurrence of this type of tubular necrosis have in common a shocklike state (or impaired renal blood supply) and trauma. The shocklike state may be caused by extensive hemorrhage, especially retroplacental or postpartum hemorrhage. The trauma may be represented by massive, crushing wounds or multiple fractures. Additional factors may be severe fluid loss as in intestinal obstruction, or diarrhea, severe infection, especially peritonitis, and severe anoxia, as with carbon monoxide poisoning. Acute tubular necrosis often coincides with, and often is inseparable from, the conditions to be discussed later.

2. *Hemoglobinuric and Myohemoglobinuric Nephrosis.* The most frequent cause of free hemoglobin in blood plasma is a transfusion accident. Myohemoglobin from dead or crushed muscles forms casts similar to those of hemoglobin in the renal tubules. The causes of hemoglobinuric nephrosis include mismatched transfusions, overheating of bank blood, long storage at room temperature; bacterial growth during storage of bank blood, and subcutaneous instead of intravenous infusion of blood. Intravascular hemolysis may be caused by burns, heat (stroke), hemolytic anemia, icterus neonatorum, sickle cell crisis, intoxications, eclampsia, or various infections. Free hemoglobin also may appear when distilled water enters the veins, either when given accidentally instead of an isotonic solution, or in the course of transurethral prostatectomy.

3. *Specific Renal Toxins.* The damage previously discussed occurs focally in any part of a nephron, but renal poisons, such as bichloride of mercury, damage those specific parts that are concerned with handling the poison.[20] The basic lesion is tubular necrosis without tubular *rhexis*. Unfortunately, large amounts of these poisons not only produce the specific changes but, because of fluid loss and circulatory collapse, also the lesions of focal ischemia. The toxic agents include the heavy metals and organic compounds such as carbon tetrachloride diethylene glycol (antifreeze), alloxan, cresol

mushroom poison, black widow poison, and serine. Other chemical toxins include phosphorus, chlorate ion, bichromate, tartrate, roentgen contrast media (especially after the high dosages used in angiocardiography[21]), and, rarely, the sulfonamides. Bacterial toxins of the staphylococcus, meningococcus, or typhoid bacillus may also cause acute anuria.

4. *Acute Glomerulonephritis.* Acute glomerulonephritis and septicemia with hemorrhagic glomerulitis may produce uremia and may be difficult to differentiate.

5. *Acute Obstruction of the Ureters.* Acute obstruction of the ureters may simulate tubular necrosis so closely that it is mentioned here, although other surgical obstructions are not discussed. An encroachment on the ureter from cancer of the bladder, uterus, or colon is a rather frequent occurrence. There may be no pain and the onset of renal shutdown may be acute. Acute obstruction of the ureters also may occur in pyelitis or in renal tuberculosis when a caseous mass blocks the ureter. Rarely, it is a complication of severe hematuria.

Sulfonamides may cause acute renal failure by allergic or toxic action with tubular necrosis, obstruction of the tubules with crystals or, most frequently, obstruction of the ureters with crystals. Only rarely, if ureteral catheterization does not lead to diuresis, will dialysis be indicated in patients with acute obstruction.

6. *Acute Pancreatitis.* In pancreatitis, oliguria of 600 to 700 ml./day is more common than is complete anuria. The tendency to improvement is slight.

7. *The Hepatorenal Syndrome.* This is not an entity. During severe hepatocellular damage, renal tubular necrosis often is found, either following the liver cell necrosis or following the primary damaging factor. Certain poisons, such as carbon tetrachloride, damage both the kidney and the liver. Cholangiolitis with icterus may be followed by glomerulonephritis.

8. *Acute Renal Failure Supervening on Existing Renal Disease.* Chronic glomerulonephritis, pyelonephritis, or polycystic renal disease may deteriorate quite suddenly into an oliguric phase because of intercurrent infection, excessive vomiting, or other metabolic disturbances. Multiple myeloma with slightly impaired renal function, suddenly may produce acute anuria for unknown reasons. Acute renal failure supervening in these conditions should be treated as any other acute renal failure, in the hope that the previous state of equilibrium may be restored.

When should treatment with the artificial kidney begin during acute uremia? When an artificial kidney and team are available, dialysis should be used early in the course of uremia. The dangers of such treatment are negligible, and the clinical course of the disease is much milder if uremia is relieved early. This is especially true in aged patients prone to pulmonary and other complications that follow prolonged bed rest. Salisbury[22] has pointed out that treatment with the artificial kidney should not be postponed until the patient is semicomatose and respiratory complications have appeared. It should not be postponed when the blood urea level is between 300 and 400 mg./100 ml.,* the serum potassium level is higher than 7 mEq./L., or the CO_2-combining power is less than 12 mEq. I tend not to wait so long; I am guided largely by the clinical conditions of the patients, which may differ immensely at identical levels of retention products. Potassium intoxication can be relieved promptly by using the artificial kidney; the electrocardiogram returns to normal during the dialysis.

Chronic Uremia

Goldner, Gordon, and Danzig[1] reported that of 20 patients with chronic uremia who had been previously treated conservatively and had shown little improvement, 7 showed remissions that lasted an average of 2 months. This clinical change often was longer than the "chemical" improvement.

In chronic uremia a single dialysis may break the spell of continuous vomiting and misery. Six hours of dialysis may be the equivalent of 6 weeks of difficult, frustrating, medical management. Some patients, seemingly in the terminal stage of uremia, have been restored to several months of useful living. If it is believed that the treatment will be worthwhile, the family of the patient must be told that the expected favorable results will be only temporary.

* The blood urea level is expressed here in milligrams of *urea*, which is 2.14 times the blood urea nitrogen.

The combination of chronic uremia with malignant hypertension usually resists all attempts at improvement.

Other Indications for Treatment with the Artificial Kidney

1. *Intoxications without Primary Nephrotoxic Actions.* Some intoxications may be treated with the artificial kidney. According to Wolf[1] bromide is more effectively removed by the artificial kidney than by the human kidney. The tubule is unable to distinguish between Cl^- and Br^-; the clearance of Br^- thus becomes a fraction of the total halide clearance and consequently is small. The artificial kidney clears bromide according to its own concentration gradient across the cellulose membrane.[14] Salicylates are removed well by dialysis.[1] Of the barbiturates,[1] some are dialyzable (phenobarbital), some are slightly dialyzable (pentobarbital), but others are almost undialyzable while bound to plasma proteins (secobarbital), and amobarbital.

2. *Dialysis as Preoperative or Postoperative Measure.* Hemodialysis occasionally is of value in preparing a patient with uremia for surgery,[4] especially if the objective of the operation is removal of the cause of the urinary suppression. In less critical cases, surgery may be performed first, and then dialysis may be undertaken if recovery is not prompt.

3. *Intractable Edema as Indication for Treatment.* Intractable edema may occur in many clinical conditions and often complicates acute or chronic uremia. The artificial kidney designed by Skeggs, Leonards, and Heisler,[6] when used as a dialyzer-ultrafilter,[1] can remove 1000 to 1200 ml. of ultrafiltrate/hr. from a patient.[23] Other types of filtering and dialyzing kidneys are less effective, according to Lunderquist,[1] but they can be used. Hematocrit determinations must be made during treatment for recognition of too rapid dehydration. During the ultrafiltration we found it useful to maintain the circulating plasma volume with dextran. Since some oliguria may occur after treatment with ultrafiltration, it is necessary to restrict the patient's fluid intake the following days. Sometimes diuresis follows a single treatment with a filtering-dialyzing artificial kidney.[23] The purely dialyzing, nonfiltering types of artificial kidneys are less effective in removing edema but, by the addition of extra glucose (1.5 to 5 per cent) to the rinsing fluid considerable amounts of fluid may be removed from the patient.[1] In this way, Lewis and associates[1] induced a 4 Kg. loss in weight in 6 hours of dialysis.

Contraindications to Treatment with the Artificial Kidney

Active bleeding formerly was thought to be the only absolute contraindication to treatment with the artificial kidney, but even this concept has been shown to be unfounded according to the wartime experience of Meroney and Herndon[24] in Korea.

Experimental Use of the Artificial Kidney

Experimentally, the artificial kidney deserves to become more widely used. It often has been used in the study of electrolyte changes. As early as 1926, Lim and Necheles[25] used the artificial kidney to demonstrate a hormone, a gastric secretory excitant, in circulating blood. Skeggs and associates[26] used it for the detection of angiotonin. Most important is that the artificial kidney in the hands of Grollman, Muirhead, and Vanatta[27] prolonged the life of nephrectomized dogs, and led to the discovery of renoprival hypertension, which has revised thinking about the etiology of renal hypertension.

Conclusion

It may be asked whether the artificial kidney has justified the expectations expressed in its name. I believe that it has, and cite 5 reasons: 1. The artificial kidney can restore the electrolyte composition of the blood plasma more rapidly than can the natural kidney. 2. The artificial kidney can reverse the clinical picture of severe, acute uremia within 24 hours; in chronic uremia it often takes 2 to 4 days to obtain optimum improvement. 3. The artificial kidney displays its ameliorating effect in patients whose serum electrolytes are not disturbed or whose serum electrolytes are not changed by dialysis. Thus, the improvement

must depend upon the removal of retention products. 4. The artificial kidney prolongs the lives of experimental animals and of human beings devoid of renal function. 5. The artificial kidney does not duplicate some of the metabolic functions of the natural kidney, but none of those functions is indispensable for the maintenance of life in the acute conditions for which the artificial kidney originally was designed.

Summario in Interlingua

Le question es si le ren artificial ha justificate le espectationes exprimite in su nomine. Mi responsa personal es affirmative, e io lista cinque rationes pro mi attitude.

1. Le ren artificial succede plus rapidemente que le ren natural a restaurar le composition electrolytic del plasma sanguinee.

2. Le ren artificial es capace a revertir le configuration clinic de sever formas de acute uremia intra 24 horas. In cases de chronic urema, meliorationes optimal es frequentemente obtenite in 2 a 4 dies.

3. Le ren artificial exerce su effectos meliorative in patientes sin disturbation o alteration dialytic del electrolytos seral. Ergo le melioration effectuate per le ren artificial debe resultar del ablation de productos de retention.

4. Le ren artificial prolonga le vita de animales experimental e de humanos sin functionamento renal.

5. Le ren artificial non exerce certes del functiones metabolic del ren natural, sed nulle de ille functiones es indispensabile pro le preservation del vita sub le conditiones acute pro le quales le ren artificial esseva originalmente construite.

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Beaven, D. W., and Murphy, E. A.: Dissecting Aneurysm During Methonium Therapy. A Report on Nine Cases Treated for Hypertension. Brit. M. J. **1:** 77 (Jan. 14), 1956.

Nine of a series of 44 hypertensive patients who came to necropsy after methonium or pentolinium therapy had dissecting aneurysm. Of the 44, 34 had malignant hypertension. Of the 34, dissecting aneurysm occurred in 6 (the other 3 cases were instances of benign hypertension). Among 89 cases of malignant hypertension not treated with the drugs mentioned only 1 case of dissecting aneurysm occurred. Among 200 control cases of benign hypertension were 6 of dissecting aneurysm. Therefore, use of the drugs was accompanied by an increase of the total incidence of dissecting aneurysm from 2 per cent (7/289) to 20 per cent (9/44)!

Review of the literature appears to confirm the impression that dissecting aneurysm is ordinarily relatively rare in malignant hypertension. As a basis of the observed increase with therapy the authors suggest the following possibilities: 1. Prolongation of life permits time for development of this complication. 2. Fluctuation of blood pressure encourages the development of dissecting aneurysm. 3. These hypotensive agents have a specific biochemical effect on the aorta.

McKUSICK

ABSTRACTS

BACTERIAL ENDOCARDITIS

Lingeman, C. J., Smith, E. B., Battersby, J. S., and Behnke, R. H.: Subacute Bacterial Endocarditis. Arch. Int. Med. **97:** 309 (Mar.), 1956.

Splenectomy is a valuable therapeutic procedure in selected cases of subacute bacterial endocarditis in which adequate and appropriate antibiotic therapy fails. Three patients, whose case histories are presented, experienced complete remissions of the disease following splenectomy. In each case, an infected infarct of the spleen had apparently been the source of the persistent bacteremia.

BERNSTEIN

Quinn, E. L., Colville, J. M., Cox, F., Jr., and Truant, J.: Phenoxymethyl Penicillin (Penicillin V) Therapy of Subacute Bacterial Endocarditis. J. A. M. A. **160:** 931 (Mar. 17), 1956.

Penicillin V was compared with penicillin G as to the concentrations attained in the blood when the 2 antibiotics were taken by mouth. It was apparent that penicillin G was absorbed faster and reached a higher concentration during the first half hour, but thereafter penicillin V reached concentrations 1.7 to 2.8 times as high as those of penicillin G. Penicillin V also gave higher blood concentrations than did penicillin G when given to 4 patients orally at 4-hour intervals over a period of weeks. Two patients with bacteremia caused by alpha-hemolytic streptococci were treated with penicillin V and sustained clinical remissions were obtained. The third patient with bacteremia caused by *Neisseria sicca* was treated with 2,000,000 units of penicillin V orally every 4 hours and with 0.5 Gm. each of streptomycin and dihydrostreptomycin intramuscularly twice daily. In a fourth patient, bacteremia caused by a *Micrococcus pyogenes* was halted temporarily, and at the time of relapse the organism was found exceptionally resistant to antibiotics. The relative toxicity of penicillins G and V given orally has not been adequately studied but prolonged administration of high oral doses of penicillin V did not result in toxic gastrointestinal manifestations in the patients studied. It was shown that probenecid will markedly increase penicillin V blood levels and the use of this agent in conjunction with penicillin V offers another approach to the problem of massive oral therapy in serious infection.

KITCHELL

Dalton, J. C., Williams B., and Atkins, L.: Staphylococcal Endocarditis after Mitral Valvulotomy. Report of Three Cases. New England J. Med. **254:** 205 (Feb. 2), 1956.

Three patients who developed bacterial endocarditis due to *Staphylococcus aureus* following valvulotomy for mitral stenosis are reported in detail. These cases occurred in a series of more than 150 patients undergoing such surgery over a period of 4 years at the Massachusetts General Hospital. Two patients received penicillin during the immediate postoperative period and 1 received chloramphenicol, although with uncertain absorption. In each patient the staphylococcus recovered was resistant to penicillin. No well-defined clinical syndrome characterized these cases. A period of nonspecific symptoms and low-grade fever preceded the abrupt onset of frank chills and fever for several weeks in 2 of the patients. Treatment was difficult and all 3 patients died, despite intensive antibiotic therapy. In 1 patient fenestration of the aortic valve was believed to be the site of a previous bacterial infection.

ROSENBAUM

BLOOD COAGULATION

Poller, L.: Coagulability and Thrombosis. Clin. Sc. **15:** 56 (Feb.), 1956.

Clotting times of venous blood were measured by using a single modification of the Silverman heparin tolerance test. Normal controls were established in 100 healthy persons. Seventy-one hospital-bed patients with a variety of medical disorders excluding thromboembolic conditions showed significantly lower clotting times than the normal controls. Another group of 40 patients who had various surgical procedures showed significantly prolonged clotting times preoperatively and shorter clotting times postoperatively. Sixty-five patients with thromboembolic conditions showed highly significant shorter clotting times within 48 hours of the onset of the disorder. Twelve patients with a variety of infections had similar acceleration of clotting times. In 43 Dicumarol-treated patients the mean clotting time was distinctly prolonged when prothrombin levels were 30 per cent or less. However, the relationship was neither linear nor constant. Indeed, accelerated clotting was present in about ½ of this group.

ENSELBERG

Adamis, D., Sise, H. S., and Kimball, D. M.: The Proconvertin Test: A Simplified Method and Its Application to the Study of Anticoagulant Processes. J. Lab. & Clin. Med. **47:** 320 (Feb.), 1956.

A simplified method for removing proconvertin from plasma by filtration through powdered wood charcoal is described. The method requires no special equipment, results in a smaller loss of prothrombin than other methods, is reliable, and therefore makes this assay widely available for clinical and other studies. Some applications of the test are illustrated.

MAXWELL

CONGENITAL ANOMALIES

Hubbard, T. F., and Koszewski, B. J.: Pulmonary Stenosis with Increased Pulmonary Blood Flow. Arch. Int. Med. **97:** 327 (Mar.), 1956.

Clinical and catheterization studies have been described in 9 cases of pulmonary stenosis with increased pulmonary blood flow. There were 6 cases of ventricular septal defect with pulmonary stenosis and 3 cases of atrial septal defect with pulmonary stenosis; there were both valvular and infundibular stenoses.

The dynamic significance of left-to-right shunts combined with pulmonary stenosis has important practical implications in the consideration of cardiac surgery for such cases. It is apparent that closure of the septal defect will do much to decrease the systolic pressure and work load of the right ventricle, since the flow across the valve is related to the square root of the pressure gradient. Prediction of the effect of opening the stenotic pulmonary valve on the degree of left-to-right shunt is not so simple. If the defect is large enough to offer essentially no resistance to flow, the flow will be determined by the relative resistance offered to flow on the 2 sides of the circulation, and decrease in the valve resistance will increase the degree of left-to-right shunt. However, in many of the cases it seems that the defect does offer resistance to flow and may be the limiting factor in determining the shunt volume.

BERNSTEIN

Counihan, T. B.: Changes in the Blood Pressure Following Resection of Coarctation of the Aortic Arch. Clin. Sc. **15:** 149 (Feb.), 1956.

Previous investigations agree that the blood pressure is reduced following resection of aortic coarctations. However, the blood pressure data have been inadequately detailed and do not permit valid conclusions as to whether normal pressures have resulted. The author made a detailed study of 20 cases. There were very great variations in blood pressure levels in each patient both before and after the operation. The changes in mean systolic and diastolic pressure were therefore examined by analysis of variance with appropriate corrections.

For the whole group the change in mean pressures after operation was 21 mm. systolic and 12 mm. diastolic. This was highly significant ($p < 0.01$). However, the residual pressures were significantly higher than normal, especially the systolic pressures. This residual hypertension could not be explained by inadequate resection, although the approach to normal pressure appeared to be enhanced by restoration of a uniform aortic caliber. It is probable that the hypertension in coarctation of the aorta is due to more than the mechanical aortic block. A possibility is the presence of developmental narrowness of the small arteries.

ENSELBERG

Ford, A. B., Hellerstein, H. K., Wood, C., and Kelly, H. B.: Isolated Congenital Bicuspid Pulmonary Valve. Clinical and Pathologic Study. Am. J. Med. **20:** 474 (Mar.), 1956.

Clinical and hemodynamic characteristics of a rare case of congenital, isolated bicuspid pulmonary valve in a 43-year-old woman are presented together with a review of the pertinent literature. In this patient, congestive heart failure developed following the healing of pulmonary tuberculosis with diffuse fibrosis. This anomaly is one of the rarest causes of pulmonary insufficiency. If a diastolic murmur is present, pulmonary insufficiency may be suspected clinically. X-ray, fluoroscopy, roentgenkymograms, and electrokymograms demonstrate the wide pulse pressure of pulmonary insufficiency. A definitive diagnosis depends on the contour of pulmonary artery pressure curves obtained by cardiac catheterization. These are closely comparable with those of aortic insufficiency. Early on the ascending limb

there occurs a notch or hesitation in pressure rise. An incisura appears in the pulmonary artery curve indicating that partial closure of the valves takes place. The fall of pulmonary artery pressure is momentarily delayed but its drop is much steeper than that normally observed. The end-diastolic pressure again approaches that in the ventricle. It appears that the duration of systole relative to the total cycle length is increased.

The 15 additional cases collected from the literature indicate that the prognosis is relatively good. The average age of the patient at death was 43.9 years. Six of the 15 cases died of causes indirectly related to the anomaly. There were 2 subjects with bacterial endocarditis and 1 with rheumatic pulmonary valvulitis. Six of 11 patients developed congestive heart failure but only in the presence of additional disease of the heart or lungs. A diastolic murmur was present in 4 of 10 patients.

HARRIS

Winchell, P., and Bashour, F.: Ventricular Septal Defect with Aortic Incompetence Simulating Patent Ductus Arteriosus. Am. J. Med. **20:** 361 (Mar.), 1956.

High ventricular septal defect with downward displacement of an aortic cusp can simulate a patent ductus arteriosus. Catheterization studies were very helpful in reaching a tentative diagnosis in the 6 cases reported. Generally there was a significant increase in the oxygen content of blood in the right ventricle as compared to the right atrium, indicating a ventricular septal defect with left to right shunt. In addition there was no significant difference between the oxygen saturations found in the right ventricle and the pulmonary artery. In each instance some degree of pulmonary hypertension was present, but in none was the pressure high enough in the right ventricle to reverse the shunt and cause cyanosis.

The differential diagnosis includes aneurysm of the sinus of Valsalva with rupture into the right ventricle, any communication between the pulmonary artery and aorta plus pulmonary valvular insufficiency, and ventricular septal defect with acquired aortic insufficiency. The most common complications of this lesion include pulmonary hypertension, congestive heart failure, and bacterial endocarditis. This lesion may be correctible by surgery in the near future.

HARRIS

CORONARY ARTERY DISEASE

Boltax, A. J., and Fischel, E. E.: Serologic Tests for Inflammation. Serum Complement, C-Reactive Protein and Erythrocyte Sedimentation Rate in Myocardial Infarction. Am. J. Med. **20:** 418 (Mar.), 1956.

Serial determinations of the erythrocyte sedimentation rate, C-reactive protein, and serum complement were obtained during 61 episodes of myocardial infarction. All 3 tests became positive in more than 90 per cent of the patients by the third day of the disease. The authors feel that there is no inherent superiority of the newer tests to the well-established procedure of the erythrocyte sedimentation rate except for study of the mechanisms of inflammation.

HARRIS

Bradley, R. F., and Bryfogle, J. W.: Survival of Diabetic Patients after Myocardial Infarction. Am. J. Med. **20:** 207 (Feb.), 1956.

In recent years coronary artery disease has been responsible for nearly one half of all deaths among diabetic patients. Preliminary observations in a large sample of hospitalized diabetic patients indicate that 40 per cent of the group have coronary artery disease. The presence of diabetes mellitus has been associated with a high mortality from acute myocardial infarction: 60.8 per cent following all attacks and 57.8 per cent after the first attack. Thus, the diabetic patient with acute myocardial infarction has a prognosis similar to that of "poor risk" cases from the general population. The high incidence of, and mortality from, myocardial infarction in diabetic women has contributed measurably to the over-all poor experience. That diabetes per se plays a major part in early mortality, particularly as a result of its effect upon women, has been shown by the 60 per cent early fatality rate for the series of women who did not have angina, hypertension, obesity, heart failure, or previous myocardial infarction. On the other hand, an early mortality of 8.3 per cent has been found for men in whom these factors were absent. Late survival of diabetic patients after the initial attack of myocardial infarction has also been decreased, since fewer than 20 per cent live 5 years and only 3.6 per cent for 10 years. Early death occurred in all of 11 diabetic subjects having marked hyperglycemia and acidosis with or without ketosis. Although each experienced "shock," it could not be shown that changes in carbohydrate metabolism were directly related to the presence of shock or to histologic changes in the liver at autopsy.

HARRIS

Choquette, G., Wasserman, F., Lisker, S., and Bellet, S.: Spontaneous Reversion of Ventricular Fibrillation to Normal Sinus Rhythm in a Case of Acute Myocardial Infarction. Am. Heart J. **51:** 455 (Mar.), 1956.

A 61-year-old white woman presented a history of advanced vascular disease of approximately 15 years' duration, resulting from hypertensive and arteriosclerotic cardiovascular disease. Following an acute posterolateral myocardial infarction, she went into sudden collapse lasting approximately 5 minutes. Ventricular fibrillation was actually recorded

over a period of 1 minute and 47 seconds and then spontaneously reverted to a normal sinus rhythm. Her convalescence was uneventful and she was discharged without any evidence of cerebral deterioration.

RINZLER

Enselberg, H.: Simplified Heparin Therapy of Impending and Acute Myocardial Infarction. Ann. Int. Med. **44:** 466 (Mar.), 1956.

Concentrated aqueous heparin was administered subcutaneously for the initial 1 to 2 weeks in 19 coronary atherosclerotic patients with an impending myocardial infarction. The results in this series were good: 2 patients developed an acute transmural infarction, a diagnosis of subendocardial infarction was made in 4, and in the other 13 apparently no infarction took place during therapy. Four of these 13 discontinued therapy prematurely, and in 3, acute infarction or death occurred within several months. In 15 patients with an acute myocardial infarction, continuous anticoagulation was maintained for the first 3 weeks, with concentrated aqueous heparin administered subcutaneously every 12 or every 24 hours. This method is simple, inexpensive, and requires few laboratory tests for control. According to the author objections to the routine use of anticoagulants in cases of myocardial infarction do not apply to heparin.

WENDKOS

Schnur, S.: Mortality Rates in Acute Myocardial Infarction. IV. The Seasonal Variation in Morbidity and Mortality. Ann. Int. Med. **44:** 476 (Mar.), 1956.

A study of 930 patients with acute myocardial infarction admitted to 2 hospitals in Houston, Texas, revealed that a significantly greater number of patients with acute myocardial infarction were hospitalized in the winter than in any other season of the year. An analysis of 3,971 deaths from acute myocardial infarction reported to the Houston Health Department from 1947 to 1952 disclosed that the largest number (29 per cent) occurred during the winter months and the smallest number (22 per cent) during the summer. These findings, which indicate that both the incidence and the number of deaths are highest in the winter, confirm earlier reports from various sections of this country, and do not support the contention of a "reversed" seasonal incidence of this disease in the South.

WENDKOS

ELECTROCARDIOGRAPHY, VECTORCARDIOGRAPHY, PHONOCARDIOGRAPHY AND BALLISTOCARDIOGRAPHY

Klensch, H.: The Force-Free Ballistocardiography (Elongation Ballistocardiography). Pflüger's Arch. ges. Physiol. **262:** 272 (Mar.), 1956.

With reference to previous work of the author and of others (especially Burger, Talbott) the technical characteristics of a new "floating" table ballistocardiograph are described. The ballistocardiograms obtained with this instrument are illustrated. The 3 main deflections, corresponding to the H, I, and J deflections of other instruments, are interpreted on the basis of differences in volume and time of blood movements to the supra- and infra-cardiac segments of the body, and therefore of displacement of the center of gravity, projected on the longitudinal axis. The physical principles of ballistocardiography are briefly reviewed.

CALABRESI

Wachtel, F. W., Lamelas, M., Grishman, A., and Donaso, E.: The Vectorcardiographic and Electrocardiographic Appearance of Left Ventricular Hypertrophy with Conduction Delay. J. Mt. Sinai Hosp. **23:** 157 (Mar.–Apr.), 1956.

This study was made on a group of 19 patients aged 61 to 80, who were in fairly good health, but presented certain electrocardiographic and vectorcardiographic features of interest. The electrocardiograms showed left axis deviation, prolonged QRS intervals, and unusual precordial patterns: small r waves and deep S waves, or RS patterns in left chest leads associated with late high R or R′ waves in right chest leads. Spatial vector studies showed that QRS vectors were superiorly oriented in all cases. The cases were clearly divided into 2 groups, one with superior and posterior orientation of vectors, and the other with superior and anterior orientation. The widening of QRS duration was due to slowing of the rate of inscription in the terminal portion.

The vectorcardiograms differ from those of right bundle-branch block and of left bundle-branch block. The electrocardiograms do not meet the criteria for left ventricular hypertrophy, though this is suggested in the extremity leads, which also showed discordant T waves in many cases. These patients had no history suggestive of myocardial infarction. The authors conclude that the vectorcardiograms in this group of patients are indicative of left ventricular hypertrophy with intraventricular conduction disturbance.

ENSELBERG

Doll, E.: The Normal Vectorcardiogram of the Newborn and Its Evolution during the First Months of Life. Ztschr. Kreislaufforsch. **45:** 99 (Feb.), 1956.

The spatial vectorcardiogram (cube system) was recorded in 125 infants 12 hours to 12 months old. The newborn shows in the horizontal plane clockwise rotation of the vector loop, which has a general direction of +60° to +100°, anteriorly. During the first through the third week the main direction changes gradually toward the left, but clockwise rotation persists until the fourth to fifth week; in

the third month all cases show counterclockwise rotation, but until the end of the first year nearly the entire QRS loop still is directed anteriorly. In the frontal plane a large section of the loop is directed to the right, and the terminal section is usually directed upward. The vectorcardiographic signs of right ventricular hypertrophy must be considered as abnormal if they persist longer than 2 months after birth.

LEPESCHKIN

Keuth, U.: Left Axis Shift on the Assumption of the Upright Position in Children. Ztschr. Kreislaufforsch. **45:** 132 (Feb.), 1956.

In 240 children 3 to 15 years old the change of QRS axis on standing up from the supine position was to the left (up to 30 degrees) in 45 per cent of the cases, to the right (up to 29 degrees) in 55 per cent. If both shoulders were pulled down in the supine position, the change on standing up was to the left in only 14 per cent; in these cases the left axis shift was due to elevation of the left half of the diaphragm by air in the stomach. These findings show that the shift to the left in the remaining 31 per cent was caused by lowering of the shoulders by gravity in the upright position, which counteracts the right axis shift caused by the concomitant lowering of the diaphragm. The lowering of the shoulders alone can cause a left axis shift up to 90 degrees, accompanied by a corresponding shift of the T-wave axis. The greater mobility of the shoulders in children accordingly can account for the greater tendency to left axis shift upon standing up in children than in adults, and also for the greater spontaneous variability of the QRS axis in children.

LEPESCHKIN

Giraud, G., Latour, H., Puech, P., and Roujon, J.: Disturbances of Rhythm in the Wolff-Parkinson-White Syndrome. Analysis of Intracavitary Electrocardiograms. Arch. mal. coeur **49:** 101 (Feb.), 1956.

Disturbances of rhythm occurring in the preexcitation (WPW) syndrome were studied in 8 cases, with the use of intracardiac leads in 6. The latter permitted the authors to ascribe the 2 principle types of the syndrome (type A and B of Rosenbaum) to preexcitation affecting the left or the right ventricle respectively. The authors maintain the concept of a hyperexcitable ventricular focus that becomes active spontaneously or by artificial stimulation, e.g., during cardiac catheterization. Occurrence of preexcitation during sinus rhythm is ascribed to electric stimulation of this center by atrial activity, whereas a mechanical stimulation by atrial contraction must be ruled out in view of persistence of preexcitation complexes during atrial fibrillation. Preexcitation occurring during rapid ectopic atrial rhythm may imitate ventricular paroxysmal tachycardia, and a number of examples of such erroneous interpretations are quoted from the literature. On the other hand, preexcitation might be simulated by the development of aberrant ventricular conduction during supraventricular tachycardia. Variations in the contour of preexcitation complexes in normal rhythm, and slow as well as rapid ectopic ones, are ascribed to changes in the cycle of excitability of the presumed hyperexcitable ventricular focus or refractoriness of the ordinary A-V conduction system occurring spontaneously or under the influence of drugs.

PICK

Brody, D. A., Erb, B. D., and Romans, W. E.: The Approximate Determination of Lead Vectors and the Burger Triangle in Normal Human Subjects. Am. Heart J. **51:** 211 (Feb.), 1956.

This report deals with the relationship of the electromotive forces of the heart and the extremity leads. The Einthoven lead connections of 6 human subjects were energized with square wave impulses of 1 Ma. of direct current, and the body surface traces of the lead fields were mapped. The lead field is the electric field produced in the body when a given set of lead connections is energized with current from an external electromotive force. Lead vectors and Burger triangles were calculated from the lead fields. The lead III field approximates the ideal lead configuration. The lead II field and especially the lead I deviate significantly from the ideal configuration.

RINZLER

Luisada, A. A., Richmond, L., and Aravanis, C.: Selective Phonocardiography. Am. Heart J. **51:** 221 (Feb.), 1956.

This report deals with a study of the problem of obtaining better phonocardiographic records of the most common murmurs whenever they are of poor amplitude. Eight normal subjects and 30 abnormal persons were studied by means of a variable band-pass filter with additional amplication. The various frequencies of the cardiac murmurs were analyzed. A band between 60 and 110 vibrations per second was found adequate for magnifying and recording murmurs caused by mitral defects; a band between 150 and 200 was adequate for those of aortic insufficiency. Based on these findings, an outline of the needs for stethoscopy, electrocardiography, and the level of the band is given for various areas of the chest.

RINZLER

Witham, A. C., and Jones, H. B.: The Relative Value of Electrocardiography and Photoroentgenography for Cardiac Surveys. Am. Heart J. **51:** 186 (Feb.), 1956.

Photoroentgenograms and 4-lead electrocardiograms were obtained on a group of 126 patients with known heart disease and 92 persons without cardio-

vascular involvement. In the interpretation of the borderline roentgenogram, mensuration was thought to be superior to inspection because of its objectivity. The cardiothoracic ratio when the internal diameter of the chest was measured at the level of the fourth anterior intercostal space, seemed to be at least as valuable a method of determining cardiac enlargement as the widely accepted Ungerleider and Clark tables for the prediction of transverse diameter. It had the added advantage of not requiring knowledge of the height and weight of the individual. In view of the wide variability in the left cardiac border among normal subjects, interpretation of the contour of the heart in the absence of definite enlargement was hazardous and disproportionately increased the number of false-positive readings. When various methods and combinations thereof were used in the interpretation of the x-rays and the electrocardiograms there was, in general, a direct relationship between the efficiency of case detection and the number of false positives noted in the control group. The ranges were exemplified by the cardiothoracic ratio with a detection rate of 71 per cent and 8 per cent false positives, and a combined technic of cardiothoracic ratio, contour reading of the x-ray, and electrocardiogram, with a detection rate of 92 per cent and 29 per cent false positives. The 4-lead electrocardiogram (I, aV_F, anterior and lateral V leads) detected a satisfactory number (83 per cent) of cardiac subjects, but had a false positive rate of 11 per cent. The reclassification of minor electrocardiographic abnormalities, however, caused an appalling fall in the detection rate, since these abnormalities occurred frequently among cardiopathies and were often the only sign of disease. If the cardiothoracic ratio is combined with the 4-lead electrocardiogram described, the misleading left cardiac border of the heart with normal transverse diameter may be ignored. Detection rate is greater than either alone (87 per cent) and false positives are at a relatively modest figure (16 per cent). The scope of the mass survey will, of course, be increased by the addition of the x-ray, since some cases of noncardiac chest disease will be detected. The electrocardiogram would, however, appear most practical for a survey limited to heart disease.

RINZLER

PATHOLOGIC PHYSIOLOGY

Huegin, F., and Verzar, F.: Work Hypertrophy of the Heart in Young and Old Rats. Pflügers' Archiv. **262:** 181 (Jan.), 1956.

In white rats left ventricular hypertrophy is produced by encircling the abdominal aorta with a silver wire of adequate diameter. Young and old animals were used with parallel series of controls. The animals were killed 5 days after the placement of the ring and the heart was divided in segments, according to the method of M. Beznak; wet and dry weights were obtained. The ratio body weight:heart weight and the quotient left ventricle:right ventricle were calculated. It is shown that the stenosis of the aorta causes an increase in weight of the left ventricle in young and old rats. The results are less significant in old animals, due to frequent right or left ventricular hypertrophy in the controls; the greatly increased number of cases with left ventricular hypertrophy in the operated animals indicates, however, that the capacity to respond with hypertrophy to the increased load is present even in the older animals.

CALABRESI

Blumberger, K., Eichinger, O., Kemmerer, G., Meiners, S., and Walz, L.: Changes of Cardiac Dynamics in Mitral Valvular Disease. Ztschr. Kreislaufforsch. **45:** 17 (Jan.), 1956.

On the basis of 37 cases the conclusion is made that after mitral valvulotomy the prolonged phase of isometric contraction becomes more normal; its component phase of changing configuration (beginning of QRS to beginning of rise of intraventricular pressure) is always decreased, while the auxotonic phase (beginning of the pressure rise to beginning of ejection) is decreased if it was prolonged previously. Creation of mitral insufficiency caused prolongation of the auxotonic phase and shortening of the ejection phase in 1 case. Mitral regurgitation shows an increased isometric phase only if heart failure is present, while the ejection phase is more often shorter than longer. Normal cardiodynamic values in the presence of marked pulmonary hypertension and a tendency to normalization after digitalis indicate a good prognosis, while marked changes of the heart dynamics with slight pulmonary hypertension can be considered as an additional indication for surgery.

LEPESCHKIN

Lochner, W., Mercker, H., and Schuermeyer, E.: The Action of Vasoactive Drugs on the Oxygen Saturation of the Coronary Sinus Blood. Arch. Exper. Path. & Pharmakol. **227:** 373 (Jan.), 1956.

The action of vasoactive drugs on the oxygen saturation of the coronary sinus blood is studied in anesthetized closed chest dogs. Coronary sinus blood is continuously drawn by pump through a catheter. The oxygen saturation is determined in a Kramer oximeter. The method used is described in detail in a previous report. The oxygen saturation of the coronary sinus blood is increased following intravenous injection of papaverine and nicotine. It is moderately increased by sympathomimetic amines; it is only transitorily increased by aminophylline. Caffein has a slight effect but only in high doses. Strophanthin is without any observable effect. Tonephin (Pitressin) decreases the oxygen saturation of the coronary sinus blood.

CALABRESI

Fletcher, G., Pender, J. W., and Wood, E. H.: Hemodynamic Effects of Ether Anesthesia and Surgery in 11 Cases. Anesth. & Analg. **35:** 18 (Feb.), 1956.

During anesthesia for abdominal or thoracic operations a few patients showed an early increase in cardiac output, related to episodes of marked excitement during the induction of anesthesia and giving way to a later decrease. In patients with uneventful induction periods, decreases occurred uniformly. The central venous pressure showed a sustained increase. The systemic arterial blood pressure decreased uniformly during the second and third hour, corresponding to both a decrease of cardiac output and of the peripheral resistance. The data suggest that ether is not a direct myocardial stimulant.

LEPESCHKIN

Courtoy, P., and Salonikides, N.: Acute Experimental Pulmonary Hypertension by Pulmonary Embolization. I. Circulatory dynamics. Acta cardiol. **11:** 52 (Fasc.), 1956.

The authors studied, in dogs, the effects of pulmonary embolization by Lycopodium granules upon the dynamics of pulmonary and peripheral circulation. When embolization involves the entire pulmonary vascular bed, marked pulmonary hypertension develops that can be shown to be independent from alterations in the central blood volume and the cardiac output and bears no relationship to the degree of associated hypoxia. No such general pressure elevation could be elicited when the emboli were confined to a limited area of the pulmonary vasculature.

On the basis of this data, it is concluded that pulmonary hypertension produced by this type of embolization has to be ascribed primarily to mechanical obstruction of pulmonary arterioles. No evidence was found in favor of the concept of a pulmo-pulmonary constrictor reflex.

PICK

Niden, A. H., and Aviado, D. M., Jr.: Effects of Pulmonary Embolism on the Pulmonary Circulation with Special Reference to Arteriovenous Shunts in the Lung. Circulation Research **4:** 67 (Jan.), 1956.

Experimental pulmonary embolism was produced in anesthetized dogs by the injection of glass beads into the right ventricle. Death occurred within 2 hours due to respiratory and circulatory failure following the injection of 5 to 8 Gm. of beads. Immediately following the injection of beads, bradycardia, apnea, and hypotension were noted in the intact animals, but not in those in whom embolization was induced after vagotomy. These immediate effects, therefore, appear to be due to a reflex mediated by the vagus. The subsequent respiratory stimulation observed was also found to be reflex in nature. This was mediated by the sensory vagus as well as by the thoracic sympathetic nerves and the aortic and carotid body chemoreceptors. Blood gas studies after embolization showed a simultaneous fall in arterial carbon dioxide and oxygen content. The anoxemia was not apparently alleviated by forced ventilation, and was only temporarily relieved by the continuous administration of 100 per cent oxygen. Studies of the pulmonary circulation after embolization showed an immediate sharp rise in pulmonary arterial pressure. Perfusion experiments indicated that this immediate rise in pulmonary arterial pressure was due to primary mechanical obstruction of vessels plus reflex vasoconstriction of pulmonary vessels mediated by the vagus nerve trunks.

The possible role of arteriovenous passages in the lungs was investigated in the perfusion experiments by passing the pulmonary venous blood outflow through a sieve after the injection of beads varying from 60 to 420 micra into the pulmonary artery. These studies showed that communications between the pulmonary artery and vein exist and are at least 420 micra in size and that these channels are opened by increasing the pulmonary artery pressure and closed by ventilating the lung with 100 per cent oxygen. This marked lability of pulmonary shunts suggests that pulmonary embolism opens them, thus aggravating the concomitant anoxemia, but at the same time minimizing the rise in pulmonary arterial pressure.

SAGALL

Leveque, P. E.: Production of Atrial Fibrillation in Dogs by Thyroid Administration and Acetylcholine injection. Circulation Research **4:** 108 (Jan.), 1956.

Atrial fibrillation could be repeatedly induced by intravenous acetylcholine in 81 per cent of dogs made thyrotoxic by the long-term administration of thyroid extract. This is in contrast to an incidence of only 30 per cent of acetylcholine-induced atrial fibrillation in normal dogs. The period of greatest sensitivity to injected acetylcholine was found to be between the sixth to twenty-fourth days of thyroid administration. It was also found that all types of atrial arrhythmias varying from simple tachycardia to sustained atrial fibrillation could be induced in the thyrotoxic dogs by intravenous injection of provocative doses of acetylcholine. The author points out that this technic provides a suitable repetitive low-cost experimental method for the evaluation of "antifibrillatory" drugs.

SAGALL

Grumbach, L.: The Initiation of Ventricular Tachycardia and Fibrillation by Procaine in the Isolated-Perfused Rabbit Heart. Circulation Research **4:** 112 (Jan.), 1956.

The initiation of ventricular arrhythmias by the injection of procaine into the perfusion fluid was studied electrocardiographically in 60 isolated rabbit

hearts perfused with Krebs-Henseleit solution in the Langendorff apparatus. After treatment of the hearts with epinephrine, procaine was found to induce a gradually accelerating ventricular tachycardia leading, in most cases, to transient or persistent fibrillation. The tachycardia started with a premature ventricular contraction coupled to an idioventricular or supraventricular impulse arising during a period of A-V block caused by the action of procaine. It consisted of a train of premature systoles coupled to the first one. When this train reached a frequency of 10 to 12 per second, ventricular fibrillation ensued. Procaine had no such effect on the untreated hearts. After production of A-V block by the severance of the bundle of His, epinephrine was found to induce only single ventricular premature systoles or trains of premature systoles of constant and relatively slow frequency. The author concludes that procaine initiates these ventricular arrhythmias in the epinephrine-treated heart by producing A-V block and also by delaying the recovery of ventricular excitability. This allows at least one epinephrine-induced premature ventricular systole (appearing because of the A-V block) to fall into the recovery phase of the preceding impulse and set up a self-sustaining accelerating tachycardia ending in fibrillation.

SAGALL

Bordet, F.: Concerning the Enigma of the "Woman Without Pulse." Arch. mal. coeur. **48:** 1105, 1955.

A 64-year-old woman showed complete absence of arterial pulsation in both arms, the blood pressure could not be obtained by the auscultatory method. There were no trophic disturbances, and the only complaint was heaviness in the arms. After 2 years small pulsations appeared; this condition persisted for 6 years, accompanied by improved pulsation. Transient hemiparesis and leg cramps were observed during this period.

LEPESCHKIN

Castelfranco, M., and Cornia, G.: Physiological Pathology and Pathogenesis of Chronic Cor Pulmonale in the Light of Experimental Findings in Man and Animals. Folia cardiol. **14:** 217, 1955.

In 1 case of extensive bullous emphysema of long duration the arterial oxygen tension was 91 per cent, the pulmonary arterial pressure 35/18 and the electrocardiogram showed only right axis deviation. Another case showed only slight emphysema but a pulmonary pressure of 116/45, an oxygen tension of 76 per cent and "P pulmonale" with right ventricular hypertrophy in the electrocardiogram; the heart output was 3.9 l/min. with a pulmonary resistance of 1332. A third case had a pressure of 70/36, a saturation of 77 per cent, a heart output of 6.8 l/min. and a pulmonary resistance of 660; the electrocardiogram showed "P pulmonale" and incomplete right bundle-branch block with tall R′. These cases illustrate the general concept that the primary cause of cor pulmonale is increased pulmonary arterial resistance; this can be accentuated by secondary arterial changes, resulting in low-output failure, or respiratory insufficiency may lead secondarily to polycythemia, hypervolemia with high output, and anoxic pulmonary constriction, resulting in high output failure.

LEPESCHKIN

Kreuziger, H., Heinecker, R., and Kemper, F.: The Influence of Smoking on the Circulation. Ztschr. Kreislaufforsch. **44:** 879, 1955.

After inhalation of the smoke of 1 cigarette in the recumbent position, the circulatory reaction was similar to that appearing after epinephrine, with very little subjective symptoms. Inhalation after standing motionless for 20 minutes caused in 13 of 17 persons vertigo, nausea, visual disturbances, and perspiration; 10 of these fainted completely. Analysis of the pulse form and velocity showed deficient venous return with marked diminution of the heart output and increase of peripheral resistance. The electrocardiogram showed tachycardia with slight S-T depression and inversion of T_{III}.

LEPESCHKIN

Valentin, H., Venrath, H., Balodimos, J., and Giovannelli, G.: The Maximal Oxygen Uptake in the Evaluation of the Heart and Circulation. Ztschr. Kreislaufforsch. **44:** 770, 1955.

According to the condition of the patient, work on the rotary electromagnetic ergometer of Knipping is started at 20–150 Watts and increased every minute by 20–30 Watts, until the oxygen uptake (registered by means of a closed-circuit spirograph) no longer increases with increased work load. This maximal uptake is expressed as a percentage of the normal maximal uptake for each age bracket. This test proved useful in the diagnosis of initial cardiac failure in the determination of the cardiac reserve in athletes and in preoperative evaluation for cardiac surgery.

LEPESCHKIN

Klepzig, H.: Studies on the Dynamic Characteristics of the Human Heart under Conditions of Increased Work. Arch. Kreislaufforsch. **23:** 96, 1955.

In 8 normal persons, 8 athletes, and 107 patients with right or left ventricular overload, the heart size, roentgenkymogram, and intracardiac pressures were measured before and during exercise in the recumbent position. In all cases without heart failure the heart size decreased without change in the ventricular filling pressure; only in those with heart failure did the heart size increase corresponding to the postulates of Starling's law. In these cases only the systolic reserve volume (Rushmer) was used to increase the stroke volume. The isometric contraction

phase (from beginning of QRS to the carotid pulse) is prolonged in athletes and in left ventricular failure; it becomes shorter after digitalis in the latter but not in the former group. Athletes and cases of heart disease with increased output develop ventricular dilatation without increase of intraventricular filling pressure; this dilatation assures an adequate systolic reserve. Increased filling pressure appears only with heart failure. Further conclusions as well as detailed findings may be obtained in the original paper.

LEPESCHKIN

Hayashi, H., and Funaki, T.: Influence of Thoracic Duct Ligation on Anaphylactic Heart Lesion (Report I). Induction of Aschoff-Body-Like Granulomata in Rabbits. Mie Med. J. **4:** 31, 1955.

In the hearts of rabbits sensitized with bovine serum whose thoracic ducts were then ligated, the 2 sorts of Aschoff-body-type granulomata which closely resembled the "myocardial interstitial Aschoff bodies" and the "myocardial Aschoff bodies" of rheumatic fever were induced by again injecting bovine serum. The characteristic mononucleated and multinucleated giant cells seen in the former granulomata are probably derived from tissue phagocytes such as tissue monocytes, histiocytes, and fibroblasts, and those seen in the latter granulomata probably are derived from myogenic elements. In this study, it was impossible to determine whether the cells of the endothelium lining the lymph vessels were transformed into the giant cells of the Aschoff-type. In the lymph vessels, characteristic lesions, including the formation of hyaline or fibrinous thrombus and hyaline degeneration of the vessel wall, were recognized in all cases.

BERNSTEIN

Hayashi, H., Funaki, T., and Morimoto, I.: Influence of Inflammatory Exudate on Anaphylactic Tissue Reaction. Induction of Cardiac Lesions Similar to Rheumatic Lesions in Rabbits. Mie Med. J. **4:** 1, 1955.

The exudate used was drawn from the pleural cavity of rabbits with turpentine-induced pleuritis. When the exudate was intravenously injected into rabbits prior to the injection with bovine serum, characteristic perivascular granulomata similar to Aschoff bodies, type C, were induced in the myocardium. When the exudate and bovine serum were injected alternately into rabbits, characteristic perivascular granulomata similar to Aschoff bodies of type B were found in the myocardium. When the injection was given rabbits prior to the injection of the exudate, characteristic perivascular granulomata similar to the Aschoff bodies of type A were produced in the myocardium. Thus, it was proposed that rheumatic-like cardiac lesions occur under the influence of antigen-antibody reaction and biological substances present in the exudate.

BERNSTEIN

Hayashi, H., Funaki, T., Inoue, T., and Seo, S.: Influence of Inflammatory Exudate on Anaphylactic Tissue Reaction (Report II). Induction of Renal Lesions Analogous to Those in Rheumatic Fever in Rabbits and the Relation between the Renal and Cardiac Lesions. Mie Med. J. **4:** 19, 1955.

In the kidneys of rabbits who received inflammatory exudate, a nonsuppurative type of inflammation similar to that found in the kidneys of rheumatic fever cases was observed in the perivascular spaces. At the same time, characteristic granulomatous lesions similar to the Aschoff bodies, type C were found in the hearts of these animals. In the kidneys of rabbits injected alternately with inflammatory exudate and bovine serum, a nonsuppurative type of inflammation similar to that described above was revealed in the perivascular spaces. In these animals characteristic granulomatous lesions which resembled the Aschoff bodies, type B, were noted in the hearts. In the kidneys of rabbits given an injection with bovine serum prior to the injection of exudate, lesions of acute diffuse glomerulitis and glomerulonephritis were found. In these animals characteristic granulomatous lesions, which resembled the Aschoff bodies, type A, were recognized in the hearts. It was concluded that the successful attempt to reproduce in animals rheumatic cardiac lesions by injecting inflammatory exudate and bovine serum explained the pathogenesis of acute rheumatic fever. At the same time, the present study indicated that inflammatory, biological substances present in the primary foci of focal infection, in addition to antigenic substance, may also play a significant role in the production of acute rheumatic heart disease.

BERNSTEIN

McMurrey, J. D., Bernhard, W. F., Taren, J. A., and Bering, E. A., Jr.: Studies on Hypothermia in Monkeys—I. The Effect of Hypothermia on the Prolongation of Permissible Time of Total Occlusion of the Afferent Circulation of the Brain. Surg., Gynec. & Obst. **102:** 75 (Jan.), 1956.

The authors were interested in determining the maximum safe period of afferent cerebral vascular occlusion in monkeys and the effect of such a procedure on the electroencephalogram. One group of animals was subjected to hypothermia without vascular occlusion, while in another both steps were carried out.

The use of hypothermia had no permanent adverse effects. The serial electroencephalogram with cooling and pentobarbital demonstrated a decrease in amplitude of all frequencies, similar to those associated

with increasing dosages of pentobarbital anesthesia alone.

The maximal period of afferent cerebral vascular occlusion that could safely be applied in hypothermic monkeys was 12 minutes. If adequate time for recovery was permitted, the procedure could be repeated.

The authors concluded that regional cerebral ischemia under hypothermia might be a solution for the surgical management of ruptured cerebral aneurysm.

ABRAMSON

PHARMACOLOGY

Fair, E.: Resuscitation after Fifty Minutes of Cardiac Arrest. Am. J. Surg. **90:** 419 (Sept.), 1955. Abstracted, Circulation **14:** 882 (Nov.), 1956.

Tripod, J., Moncada, A., Jacques, R., and Wirz, E.: Pharmacologic Action on Isolated Heart of Mammals of Different Metabolites, Particularly of Acids of Intermediary Carbohydrate Metabolism. Arch. internat. pharmacodyn. **104:** 12 (Dec.), 1955.

The effects on coronary flow and cardiac activity of a series of metabolites have been examined using the isolated rabbit heart perfused according to Langendorff. The substances tested are lactic acid, glycolytic coferments (muscle and yeast adenylic acid, ATP), metabolites of the citric acid cycle, metabolites of fats, and other intermediary metabolites. Concentrations in the physiologic range or higher have been used. The coronary flow, the cardiac rate, and the amplitude of systole have been studied. In "physiologic" concentration adenylic acid and ATP dilate the coronary vessels and inhibit the cardiac activity; of the other substances tested only succinic acid shows some cardiac stimulant effect and coronary vasoconstriction. In higher concentrations most of the acids of intermediary metabolism tested depress the cardiac activity and cause coronary constriction. The 2 effects, on cardiac activity and on coronary flow, can be separated for some of these substances. Although the significance of this observation remains uncertain the authors suggest that normal metabolites may influence the cardiac activity and especially the coronary flow; also that they may modify the effect of drugs, especially in heart disease.

CALABRESI

Casella, C., and Marchetti, G.: Effects of Procaine Amide and Quinidine on the Excitability and Refractory Period of the Frog Heart. Acta. cardiol. **11:** 130 (Fasc. 2), 1956.

The authors studied on the isolated spontaneously beating apex of frog hearts the behavior of the refractory period under the influence of quinidine and procaine amide. These experiments revealed that quinidine exerts a much more pronounced depressive action on excitability than procaine amide. Thus the chronaxie was found to be about 10 times longer with quinidine compared with procaine amide and hardly any prolongation of the ventricular refractory phase was observed by the authors by the latter. The results of these experiments are discussed with regard to the action of the two drugs in the management of clinical arrhythmias.

PICK

Voskian, J., Assali, N. S., and Noll, L.: Hemodynamic Effects and Clinical Application of a Mixture of Veratrum and Rauwolfia Alkaloids. Surg., Gynec. & Obst. **102:** 37 (Jan.), 1956.

The authors studied the hemodynamic effects and clinical application of a mixture of veratrum and Rauwolfia alkaloids in 38 pregnant patients. Of this number 4 were normotensive, 27 were in preeclampsia, 4 were suffering from convulsive toxemia, and 3 had essential hypertension.

It was found that the intravenous injection of 0.1 mg. of veratrum alkaloids and 2.5 mg. of reserpine resulted in an average fall of 38 per cent systolic and 40 per cent diastolic blood pressure. The fall in pulse rate averaged 35 per cent. For the most part, cardiac output remained unchanged, while total peripheral resistance was significantly reduced. The initial fall in blood pressure was accompanied by a reduction in both renal plasma flow and glomerular filtration rate, but later a progressive rise in both occurred.

The incidence of side effects that are peculiar to veratrum and to Rauwolfia preparations was significantly less following administration of a mixture of the 2 drugs. It was therefore concluded that this combination has a number of advantages that make it an excellent adjunct in the therapy of hypertensive diseases.

ABRAMSON

Reisner, E. H., and Morgan, M. C.: Thrombocytopenia Following Acetazolamide (Diamox) Therapy. J. A. M. A. **160:** 206 (Jan.), 1956.

The occasional occurrence of thrombocytopenia following the use of sulfonamide drugs has been well documented. The authors report a case of thrombocytopenic purpura in an 85-year-old white man who had been on Diamox 3 weeks prior to the onset of symptoms. In vitro studies indicated that platelets disappeared more rapidly in his plasma in the presence of Acetazolamide; but Acetazolamide did not have this effect when normal plasma was used. It was considered, therefore, that the drug combined with some factor peculiar to the patient's plasma to produce an antiplatelet agglutination.

KITCHELL

Schneider, E. M., and Clark, M. L.: Hyperchlorhydria Induced by Intravenous Reserpine. Am. J. Digest. Dis. **1:** (N.S.), 22 (Jan.), 1956.

One of the side effects of the administration of reserpine is hyperchlorhydria. To test whether this effect is a central one or a local peripheral one, the effects of the simultaneous administration of reserpine and various parasympathetic blocking agents on gastric acid secretion were noted. There was no blocking effect upon the hyperchlorhydria induced by reserpine when atropine, banthine, and epinephrine were administered simultaneously with reserpine. Dosage, route of administration, and technic of obtaining gastric juice were carefully controlled. The authors suggest that these results indicate that this hyperchlorhydria is a local or hormonal rather than a central effect.

HARVEY

Chaney, R. H., and Maronde, R. F.: Clinical Evaluation of Diuretic Mersoben. Am. J. M. Sc. **231:** 26 (Jan.), 1956.

Mersoben is described as an aliphatic compound dispensed as a lyophilized, amorphous, hygroscopic solid in 2-ml. vials which is dissolved in distilled water for parenteral injection. The preparation was administered in 2 concentrations of mercury, the first providing 50 mg. and the second 40 mg. of this element. Comparison of their actions was made with that of Mercuhydrin. In 62 patients given the 50 mg. of mercury Mersoben, 28 lost over 3 pounds within 24 hours; in 23 patients given the 40 mg. mercury salt, a significant loss of edema occurred in 15. In 32 patients given the Mercuhydrin (39 mg. of mercury in organic combination) 20 had a similar diuretic response. Previous diuretic therapy in some patients makes the response difficult to evaluate, since the diuresis is usually more prompt in untreated edematous patients. The side effects observed after Mersoben injections were minimal, consisting of infrequent local pain, rash, nausea, and vomiting; there were no evidences of renal or systemic toxicity. It was concluded that Mersoben is a potent diuretic containing a minimum of mercury.

SHUMAN

Reiter, M.: Influence of Rate, of Sodium Loss, and of Strophanthin on the Strength of Systole and Alkali Content of the Cardiac Muscle. Arch. Exper. Path. & Pharmakol. **227:** 300 (Jan.), 1956.

The intracellular potassium and sodium of right ventricular cardiac muscle of rats is measured in fresh preparations and after incubation at 37 C. Stimulation of a bundle of myocardium at a fast rate produces at first, loss of sodium and, later, loss of potassium; the strength of systole increases. Loss of sodium produced by decrease in concentration of the ion in the external solution, without change in intracellular potassium, increases the strength of contraction of the preparation. The positive inotropic effect of strophanthin is independent of changes in intracellular sodium and potassium concentration; the inward and outward movements of potassium are decreased, however. When contracture is produced by toxic doses of strophanthin, the intracellular potassium is decreased and sodium is increased.

CALABRESI

Crossley, C. F., and Wycoff, C. C.: Digitalis in Anesthesiology. Anesth. & Analg. **35:** 48, (Feb.), 1956.

The signs of acute myocardial failure during anesthesia are peripheral stasis, weak rapid pulse, narrow pulse pressure and, especially, elevated venous pressure; a simple device for measuring this is described. Intravenous Cedilanid rapidly counteracts myocardial failure and has been seen to regularize presumable atrial fibrillation within 25 minutes and control hypotension in 5 minutes. Previously digitalized patients receive 2 ml. when failure appears and another 2 ml. in 15 minutes if necessary; 4 ml. is given in the same way in nondigitalized patients in critical failure, while in noncritical failure, 2 ml. are given every 15 min. until adequate improvement appears or up to a total of 8 ml. No ill effects other than minor ones have been observed from rapid digitalization.

LEPESCHKIN

Smallwood, W. C., and Matthews, H. L.: Systemic Reactions to a Mercurial Diuretic (Mercaptomerin). Lancet **1:** 121 (Jan. 21), 1956.

In 3 patients allergic reactions occurred and in 1 hemorrhagic colitis. Pyrexia was a striking feature.

McKUSICK

Schreiner, B.: Pharmacological Effects on Intramuscular Pressure in Relation to the Treatment of Deficient Orthostatic Circulatory Regulation. Ztschr. Kreislaufforsch. **44:** 806, 1955.

In 27 cases intramuscular injection of "Carnigen" (a sympathomimetic drug dissolved in an organic extract containing nucleosides) always increased the intramuscular pressure with a maximum about an hour after injection. This increase was especially marked if this pressure was low previous to injection, and was of longer duration than when the sympathomimetic drug was injected alone. In cases showing orthostatic changes in T and S-T of the electrocardiogram, the degree of these changes as well as the subjective complaints decreased and the intramuscular pressure increased after continuous medication with "Carnigen" for 7 or 14 days, but both changes were not always parallel.

LEPESCHKIN

Cotten, M. deV., and Bay, E.: Comparison of the Cardiovascular Properties of a New Nonbarbiturate Intravenous Anesthetic Agent with Those of Thiopental. Anesthesiology **17:** 103 (Jan.), 1956.

Dolitrone, a new nonbarbiturate anesthetic agent

produces, after intravenous administration in intact animals, a rapid and complete general anesthesia closely similar to that produced by thiopental. Thirty milligrams per kilogram of Dolitrone are about equal in anesthetic potency to 20 mg./Kg. of thiopental. In dogs, the effect of Dolitrone and of thiopental on the blood pressure, the ventricular contractile force, and the electrocardiogram are limited and essentially similar in equivalent anesthetic doses. Both drugs produce a marked increase in the heart rate of the dog. After both Dolitrone and thiopental, there is a moderate increase in the incidence of epinephrine—induced arrhythmias, but fewer arrhythmias are produced by epinephrine following Dolitrone than by following thiopental. With equivalent anesthetic doses, the duration of anesthesia is about the same for both drugs. In the nonpremedicated animal, full anesthetic doses of either drug does not seriously reduce the respiratory rate, but in animals premedicated with morphine thiopental frequently produce respiratory arrest while Dolitone is well tolerated. In most cases recovery from Dolitrone is smooth but in some animals an interval of intense excitement occurs during the recovery phase of anesthesia. This is not observed in the recovery phase from thiopental administered to the same dogs.

SAGALL

Moyer, J. H., and McConn, R.: Renal Hemodynamics in Hypertensive Patients Following Administration of Pendiomide. Anesthesiology **17:** 9 (Jan.), 1956.

Observations are reported on renal hemodynamics and on water and electrolyte excretion studies made on 18 patients with hypertension after reduction of blood pressure by continuous intravenous infusion of Pendiomide. As the blood pressure was reduced to normotensive levels, depression of the renal blood flow and glomerular filtration rate was found. Associated with this, there was a marked and maintained reduction in the excretion rates of water and sodium. With maintenance of blood pressure reduction for 3 hours or more by continuous Pendiomide infusion, depression of glomerular filtration rate and reduced excretion rates of sodium and water continued, but the renal blood flow tended to return toward the control levels. The responses observed in the hypertensive patients were qualitatively similar to the responses of normotensive individuals reported previously, but the degree of alteration was more marked in the hypertensive patients.

SAGALL

Schimmler, W.: Measurement of the Cerebral Circulation with T-1824 (Evans Blue) in Man. Ztschr. Kreislaufforsch. **45:** 47 (Jan.), 1956.

One to 5 mg. of the dye (Evan's Blue) are injected rapidly into the internal carotid artery, and the dye dilution is calculated according to Hamilton from the average values of blood taken from both superior jugular bulbi. The average cerebral circulation determined by means of this method in 5 cases was 882 ml./min. while the average oxygen uptake was 54 ml./min.

LEPESCHKIN

Friedman, B., Daily, W. M., and Wilson, R. H.: Studies on Mitral Valve Function. Effect of Acute Hypervolemia, Premature Beats and other Arrhythmias. Circulation Research **4:** 33 (Jan.), 1956.

The authors studied the effect of certain arrhythmias and hypervolemia on the competence of the mitral valve in anesthetized mongrel dogs whose hearts were exposed by thoracotomy. The experimental method employed consisted of injecting 5 per cent sodium chloride into the left ventricle and detecting its presence in the left atrium within 1 or 2 heart beats following injection and before recirculation by means of the changes induced in the impedance of blood that could be recorded from a conductivity cell placed in the left atrium. This method does not require the withdrawal of blood samples and may be repeated at frequent intervals.

Evidences of mitral valve regurgitation were found in approximately 20 per cent of the control dogs in the absence of significant changes in atrial pressure tracings. No definite explanation for this was apparent, but the possibilities considered were that functional mitral valve insufficiency was produced by the minor hemorrhage incidental to operation, the open pericardium and the undetected hypoxia.

Mitral insufficiency was observed regularly in association with ventricular flutter and fibrillation, frequently with ventricular premature beats and less often with ventricular tachycardia. With acute hypervolemic states and ectopic rhythms of atrial origin, mitral insufficiency was produced only under conditions of severe ventricular muscle strain or failure.

SAGALL

Read, R. C., Lillehei, W., and Varco, R. L.: Cardiac Resuscitation and Neurologic Tolerance to Anoxia. Circulation Research **4:** 45 (Jan.), 1956.

Temporary circulatory arrest was induced in 96 anesthetized mongrel dogs by means of occlusion of the superior and inferior vena cava for periods varying from 6 to 10 minutes. Ninety-four dogs recovered from this procedure and form the basis of this report.

Ventricular fibrillation did not develop during the period of venous occlusion, but occasionally was noted immediately following filling of the heart. The incidence of this arrhythmia was markedly reduced by the prevention of cardiac dilatation with immediate effective cardiac massage during the period of resuscitation, and by the avoidance of epinephrin.

With immediate cardiac resuscitation by massage about one half the dogs survived 10 minutes of venous inflow occlusion without permanent neurologic sequelae. When the period of occlusion was reduced to 8 minutes, a uniform survival was obtained and only a rare animal showed lasting damage. Ventilation of the lungs with oxygen during the period of inflow stasis resulted in an insignificant improvement in the number of animals without central nervous system changes. The incidence of brain damage was found to be unaffected by the administration of heparin in various doses.

SAGALL

Hopkins, W. A., Skandalakis, J. E., and Davis, M. B.: The Treatment of Cardiac Arrest. Geriatrics **11:** 1 (Jan.), 1956.

The cause of cardiac arrest are hypoxia, hypercapnea, reflex vagotonia, and drug sensitivity. The authors believe that all hospitals and all teaching services should make cardiac resuscitation a requisite course for their house staff. Failures in relieving cardiac arrest arise from 2 major causes: hesitancy to carry out the necessary procedures and inadequate application of cardiac massage. In a detailed study of 50 patients with cardiac arrest seen in 8 hospitals in the Atlanta area over a period of 2 years; 17 are living and well; 2 are living, but have evidence of cerebral damage; and 1, a child, has severe cerebral damage. Thirty died, 11 were not resuscitated at all; the remainder were resuscitated but died from other causes, predominantly cerebral damage. The injection of epinephrine into the chamber of the left ventricle and electric defibrillation are also suggested in therapy.

RINZLER

Alexander, R. S.: Reflex Alterations in Venomotor Tone Produced by Venous Congestion. Circulation Research **4:** 49 (Jan.), 1956.

The venomotor tone was determined in anesthetized dogs from observations of the venomotor index calculated from distensibility diagrams obtained from injections into the veins of an exteri orized loop of intestine. Partial occlusion of the thoracic inferior vena cava or of the mitral orifice resulted in acute congestion of the abdominal vena caval system and tended to produce an intense vasoconstriction associated with the precipitous fall in arterial pressure due to the acute reduction of venous return to the left ventricle. The latter effect was compensated for by the introduction of a reservoir system into the femoral artery that stabilized the blood pressure. The studies reported showed that a rise in inferior vena caval pressure was associated with a reduction of the venomotor index —an indication of relative venodilation. This change in venomotor tone was the result of a reflex mechanism that was mediated by vagal afferents and inhibition of sympathetic efferents. Central congestion produced by mitral stenosis produced a similar response. These veno-venous reflexes would appear to contribute to homeostasis of the vascular system by aiding in the adjustment of venous capacity to the venous load.

SAGALL

Garb, S., Scriabine, A., Penna, M., and Fujimari, H.: The Effects of Reduced Glutathione and Related Substances on the Threshold of Irritability of Mammalian Ventricular Muscle. J. Pharmacol. & Exper. Therap. **115:** 300 (Nov.), 1955.

Previous studies have shown that the various aspects of cardiac muscle function can be affected differently by drugs. This suggested the possibility that different substrates and metabolic cycles may be involved in the production of energy for the various functions of cardiac muscle. It had been found that reduced glutathione lowered the threshold of irritability more than any other substance reported before. Therefore, the actions of glutathione and related substances were investigated.

The cat papillary muscle preparation (Cattell and Gold, 1938) was stimulated at a rate of 60 per minute. Contractile force and threshold of irritability were measured. Test substances were added to the bath and their effects noted.

Reduced glutathione, in concentrations above 25 mg./100 ml., lowered the threshold of irritability but did not change contractile force. Cysteine showed a lesser effect on the threshold of irritability but a greater effect on contractile force. Glycone lowered the threshold of irritability slightly but increased contractile force more strikingly. DL-Methionine only increased contractile force. BAL and copper sulfate gave varied results depending on the dose. Oxidized glutathione and sodium glutamate had no significant effect on threshold of irritability or contractile force.

Reduced glutathione had a greater effect on threshold of irritability than any of its components. Since cysteine has a similar effect to a lesser extent, and since methionine does not significantly affect irritability, it may be deduced that the sulfhydryl group is essential, but that it is most effective when part of glutathione. The mechanisms of action of reduced glutathione are not known.

The significance of these findings is that various aspects of heart muscle function can be affected differently by different substrates. This suggests that the metabolic cycles furnishing energy for cardiac irritability may be distinct from those furnishing energy for the contractile process. Reduced glutathione lowers threshold of irritability more than Isuprel, which is useful in clinical heart-block, so that it too may prove useful in this condition. The effects of methionine, glycine, and cysteine on contractile force suggest that in the cat the amino acids may be more important substrates for

myocardial contraction than glucose, which does not affect the cat papillary muscle preparation.

WECHSLER

West, T. C.: Ultramicroelectrode Recording from the Cardiac Pacemaker. J. Pharmacol. & Exper. Therap. **115:** 283 (Nov.), 1955.

The advent of the ultramicroelectrode technic makes it possible to observe the electric events in membranes of single cells in a great variety of tissues. Previous work in turtle hearts with this method reported, in the pacemaker area, a steadily rising prepotential during diastole ending in sharp depolarization with electric systole. A similar configuration was observed in mammalian Purkinje tissue. This report describes the electric localization of pacemaker activity in surviving atria of rabbits.

Rabbit atria were suspended between hooks in Tyrodes solution at 37 C. Exploration for cellular potentials was conducted over the exposed surface of the right atria by means of an ultramicroelectrode. Membrane potentials were recorded from the pacemaker area and from a cell outside the pacemaker. The area where earliest depolarization occurred was located.

Outside the sinoatrial node, atrial myocardial cellular potentials were all qualitatively similar (rapid depolarization, relatively rapid concave repolarization, and absence of diastolic prepotential). In the pacemaker area, diastolic prepotentials exist, depolarization with electric systole is relatively slow, and repolarization follows a slow convex course. The cells depolarize earlier, overshoot is usually absent, and the average value of the resting potential is lower than elsewhere in the atrium.

Drugs or procedures capable of affecting atrial rate often disturbed time relationships between potentials in the pacemaker region. Acetylcholine, when added to the nutrient solution, temporarily shifted pacemaker function to some other site and caused a change in the configuration of the original pacemaker potential. Epinephrine and cooling of the chamber produced similar results.

These results show the prepotentials observed in pacemaker cells are not propagated out of the pacemaker region. In addition, the anatomic region termed the pacemaker area is indeed the site of impulse formation. Shifts in pacemaker locus have been shown to occur following the application of drugs.

WECHSLER

Auinger, W.: Changes of the Amplitude of the First Heart Sound under the Influence of a Digitalis Glycoside in Absolute Arrhythmia. Ztschr. Kreislaufforsch. **44:** 889, 1955.

In 15 decompensated patients with absolute arrhythmia, the intensity of the first heart sound usually decreased as the duration of the preceding diastolic pause increased; in some cases it showed a temporary increase with further increase of the pause between 0.4 and 0.8 sec. Thirty minutes after intravenous injection of 0.6 to 0.8 mg. of Cedilanid (lanatoside C) the amplitude increased in cases showing a slight decrease of the heart rate and decreased in those showing a marked decrease. However, within each range of diastolic pauses the amplitude nearly always showed an increase. The 3 cases that showed a decreased amplitude at comparable diastolic pauses showed a marked fall of the heart rate; in these cases this decrease was parallel to the increase of the pause preceding the preceding pause. The interval from beginning of QRS to the beginning of the carotid pulse decreased in all cases, but showed no definite trend if similar prededing pauses were compared; the decrease was accordingly due to the fall of the heart rate.

LEPESCHKIN

Villamil, A., Clavijo, J., Franco, R. J., Buzzi, R. H., and Abelardi, U.: Circulatory Function in Artificial Hibernation. Acta physiol. latinoam. **5:** 104, 1955.

Artificial hibernation has been induced in 12 subjects by administration of neurolytic doses of phenothiazine derivatives, preliminary to the application of cold by ice bags. Rectal temperatures below 30 C. were reached and maintained without the complications of ventricular fibrillation or of severe arrhythmias, even during cardiac catheterization. In 4 cases the circulatory function was thoroughly studied. Parallel to the fall in body temperature, the cardiac and respiratory rates and the arterial and venous blood pressures diminished. The blood volume and the hematocrit did not change significantly. The oxygen consumption decreased and the arteriovenous oxygen difference increased; hence, the cardiac output and the work of the heart were reduced. The arterial oxygen saturation was slightly decreased. The mechanism of the heart was regular and bradycardic; however, sinus tachycardia and premature beats may appear during the induction. Except for marked prolongation of the Q-T interval the electrocardiographic contour was normal.

CALABRESI

PHYSIOLOGY

Baldrighi, V., Montemartini, C., and Calderoni, A. G.: On the Cardiac Ejection Curve. Boll. Soc. ital biol. sper. **31:** 349, 1955.

Using a low frequency instrument of their design, the authors compare the ballistocardiogram with the aortic flow curve in 7 dogs. In accord with previous studies, it is concluded that the ballistocardiogram is the third derivative of the ejection curve of the heart. The changes of the ballistocardiographic curve in man in inspiration and in expiratory arrest also indicate that the ballistocardiogram is determined by the velocity of ejection and therefor

is influenced by the diastolic volume and by the stroke volume of the left ventricle.

CALABRESI

Miektiewski, E.: Chemoreceptors in Blood Vessels of the Ear of Rabbits. Arch. Int. Pharmacodyn. **104:** 373 (Jan.), 1956.

End-organs sensitive to various chemical stimuli are found in the blood vessels of the ear of rabbits. The ear, completely separated from the body, except for the nervous connections, is a convenient preparation for the study of the chemoreceptors. Nicotine causes a fall of systemic pressure; acetylcholine has a similar effect but also a much stronger influence on respiratory movements that are accelerated and increase in amplitude. The effect of epinephrine on blood pressure is also similar to that of nicotine. Section of the vagus or sympathectomy in the neck does not abolish the depressor reflex. This reflex however, can be inhibited by local anesthesia.

CALABRESI

Scholander, P. F. and Schevill, W. E.: Counter-Current Vascular Heat Exchange in the Fins of Whales. J. Appl. Physiol. **8:** 279 (Nov.), 1955.

Whales swimming about in icy waters can maintain a normal mammalian body temperature in spite of their large, thin, and vascular fins. Anatomic and perfusion studies reveal that all arteries entering the fins and flukes are surrounded by a trabeculate venous channel. The arteries drain into these and also into superficial simple veins. The artery within the venous channel is interpreted as a heat-conserving counter-current exchange system. This impressive example of bioengineering for a successful existence in a heat-hungry environment is present in man in a rudimentary form. Bazett and his coworkers found that, in man, the brachial artery could lose as much as 3 C. per decimeter to the 2 venae comitantes.

AVIADO

Cyvin, K., and Retterstøl, N.: Some Remarks on Cardiac Output Estimation. Acta med. Scandinav. **152:** 465 (July), 1955.

This report is concerned with a number of recommendations to be followed in the use of dye technics to measure cardiac output. It is mentioned that the dye, T 1824, alters with storage and should be protected against light and air. The dye staff available in recent years is purer than that available previously, making a 0.25 per cent solution in saline quite satisfactory. To prevent a part of the dye injected into the antecubital vein from being retained in the cephalic vein, a venous cannula is used followed by rinsing of the vein with saline. Correction of cardiac output estimations by means of hematocrit readings is said to introduce a considerable error. This may be avoided by using for comparison in each tube a known solution of the dye in the blood. The importance of clear plasma is emphasized, and measures helpful in obtaining it include careful rinsing of the tubes, dry heparinizing, prevention of coagulation in the puncture needle, prevention of temperature variations, and cautious centrifugation with a final rotation speed of 3,000 r.p.m. The authors believe that the Pulfrich photometer has several advantages and employ 10 mm. microcuvettes, thereby using very small amounts of plasma and avoiding the need for dilution of the plasma. The S 61 filter, which corresponds to a wave length of 620 mm., is said to give a high degree of accuracy, since the top of the absorption curve of T 1824 corresponds to this wave length.

ROSENBAUM

RHEUMATIC FEVER

Harris, T. N., Friedman, S., Needleman, H. L., and Saltzman, H. A.: Therapeutic Effects of ACTH and Cortisone in Rheumatic Fever: Cardiologic Observations in a Controlled Series of 100 Cases. Pediatrics **17:** 11 (Jan.), 1956.

A very thoughtful and excellent controlled study is presented involving 100 patients with acute rheumatic fever treated with aspirin, ACTH, and cortisone. In each of the 3 treated groups there were approximately 33 patients, classed approximately evenly in regard to onset of attack, severity, and presence of carditis. The study extended over a 4-year period with follow-up studies extending from 2 to 6 years after treatment. Very careful analyses of the appearance and disappearance of murmurs, degree of transmission of apical systolic murmurs, development of pericarditis, changes in cardiac rhythm, presence of congestive failure, and death in the 3 groups are presented. A thoughtful analysis of the limitations of the study is also presented.

It is concluded that ACTH and cortisone do not have any measurably greater beneficial effect upon the course of rheumatic carditis than treatment with aspirin.

HARVEY

Harris, T. N., Needleman, H. L., Harris, S., and Friedman, S.: Antistreptolysin and Streptococcal Antihyaluronidase Titers in Sera of Hormone-Treated and Control Patients with Acute Rheumatic Fever. Pediatrics **17:** 29 (Jan.), 1956.

Controlled studies were made to determine the effect of ACTH and cortisone on antibody levels of streptococcal antihyaluronidase and antistreptolysin O in patients with acute rheumatic fever. Serial sera were obtained from patients. Antihyaluronidase antibody was determined by precipitation of a mucin clot in a medium of potassium hyaluronate from human umbilical cord, hyaluronidase obtained from a supernate of a lyophilized concentrate of streptococcus culture, and patient serum. Antistreptolysin O titers were measured by the Todd method. These studies showed there was a fall in antihyaluronidase

and antistreptolysin antibodies in all patients but that the fall in time in the ACTH and cortisone-treated patients was significantly greater than in the aspirin-treated control group.

HARVEY

Kalliomäki, L.: Therapy of Rheumatic Fever. Comparison of Results Obtained with Salicylates, Cortisone or Corticotrophin, Phenylbutazone, and a Combination of Sodium Salicylate, Para-aminobenzoic Acid and Cortisone. Acta med. scandinav. **152:** 473 (July), 1955.

The results of treatment of 17 patients with rheumatic rever with phenylbutazone and 14 patients with a combination of sodium salicylate, para-aminobenzoic acid and cortisone are reported and compared with earlier reports from the same observers concerned with the results of treatment of rheumatic fever with salicylates alone and with cortisone or corticotrophin. No significant differences were observed in the primary results of treatment. During the first 2 weeks of treatment the most abrupt fall in sedimentation rate occurred in the patients receiving combination therapy. There was also a definite diminution in "rebound phenomenon" in the group receiving combination therapy when the cortisone was stopped. The febrile period was of equal duration in the groups receiving phenylbutazone or combination therapy with the exception that phenylbutazone had a somewhat greater antipyretic effect. Neither phenylbutazone or combination therapy seemed capable of inhibiting the recurrence of rheumatic rever. The author believes that in the choice of therapy the major emphasis should be upon the patient's tolerance, possible complications, cost of drugs, and ease of administration, since no significant differences in response to the various drugs have been demonstrated.

ROSENBAUM

ROENTGENOLOGY

Real, A. P.: An Index for Aortic Dilatation. Rev. españ. cardiol. **9:** 177, 1955.

An index suggestive of aortic dilatation is obtained by dividing the width of the thorax at the level of the upper border of the vascular shadow in the frontal roentgenogram by the total width of this shadow. Under normal conditions the index is greater than 3.7. Values of 3.1 to 3.6 correspond to aortic dilatation of the first degree, and are usually found in persons with hypertension under 50 years of age and in older subjects without hypertension. Values of 2.5 to 3 correspond to a second degree of dilatation, while values less than 2.5 are considered as indicating third degree dilatation. These values are usually found in hypertensive subjects over 50 years; second degree dilatation is sometimes found also in older persons without hypertension. In young persons the right border of the vascular shadow is formed by the superior vena cava, but this does not cause the values of the index to become abnormal. This index can be applied only if the thorax is of normal configuration and in the absence of venous hypertension.

LEPESCHKIN

SURGERY AND CARDIOVASCULAR DISEASE

Baker, C. G., and Campbell, M.: The Results of Valvotomy for Aortic Stenosis. Lancet **1:** 171, (Jan. 28), 1956.

Of 16 patients in whom valvotomy was performed, 6 died and only 5 achieved a good result, 1 of these dying within 18 months, however. Aortic regurgitation is likely to be produced and is a leading reason for failure of the operation. The great majority, possibly all, of the cases of advanced valvular obstruction show appreciable calcification, a factor that makes surgery difficult.

Most of the patients were men between 40 and 50 years old. The oldest patient was a 61-year-old medical man who had had his first bout of syncope at the age of 27 years. Two were children, ages 6 and 16 years, with congenital aortic stenosis.

It is concluded that the surgery of aortic stenosis is presently in an unsatisfactory state.

MCKUSICK

Ada, A. E. W., and West, J. P.: Excision of Aortic Aneurysms with Restoration of Circulation by Aortorrhaphy or Arterial Graft. Ann. Surg. **143:** 57 (Jan.), 1956.

The authors reported the results of treating 5 aortic aneurysms surgically. In 2 patients, the lesion was sacciform and involved the thoracic aorta, and in both instances a successful result was obtained after excision of the sac and repair of the defect in the wall of the aorta by suture. In the 3 other individuals, a fusiform aneurysm was present in the abdominal aorta. In each case the lesion was excised and the circulation was restored by the use of homologous bifurcation grafts.

Following operations, all the patients were relieved of their symptoms and resumed normal activities.

ABRAMSON

Feil, H., Pritchard, W. H., Hellerstein, H. K., Watts, R. W., Hornberger, J. C., and Helfrich, H. M.: The Beck Operations for Coronary Heart Disease: An Evaluation of 63 Patients Selected for Operation. Ann. Int. Med. **44:** 271 (Feb.), 1956.

The Beck I operation consists of abrasion of the epicardium and lining of parietal pericardium, application of an inflammatory agent to these surfaces, partial occlusion of the coronary sinus, where it enters the right atrium, and grafting of parietal pericardium and mediastinal fat to the surface of

the heart. The Beck II operation has as its purpose the arterialization of the coronary sinus and consists of 2 stages and occasionally 3. This interesting surgical approach for the relief of patients with arteriosclerotic heart disease is to be commended, although its clinical application must be limited until statistical proof of its efficacy in the cases operated upon has been established. Cooperation between physiologist, experimental surgeon, and physician will determine the best method of augmenting coronary arterial supply and its application to man. The Beck I operation, while still an experimental procedure, may be reserved for patients who are invalided by pain not relieved by medical therapy. Coronary disease, when manifested by angina of effort or emotion, is usually severe. Improvement from any therapy, of course, depends on the remaining intact musculature receiving an augmented blood supply. The data in this small series do not permit any conclusions. The Beck II operation also has a valid experimental background and is effective in enabling the dog to withstand coronary artery ligation. In man, the operation is difficult to perform and lengthy. The operative mortality was approximately 25 per cent. The operation, in addition to its production of intercoronary vessels, actually adds a burden to the heart and circulation by increasing cardiac output and blood volume. In a few instances there was increase in blood pressure and in heart rate. In some patients, cardiac failure was induced and the coronary sinus had to be ligated. This operation, then, in its present state of development, should be held in abeyance.

WENDKOS

Di Matteo, G., and Manfredi, D.: A New Method for the Experimental Replacement of the Aortic Arch. Polyclinico, sez. prat. **63:** 105 (Jan.), 1956.

The authors submit a new technic that allows the performance of a complete graft of the aortic arch with termino-terminal sutures, by temporary deviation of circulation from the apex of the heart to the descending aorta. This method offers advantages in the technical execution of sutures and in the orientation and diameter of the anastomotic segments, with the result of a correct restitution of the anatomic condition.

CALABRESI

Vaysse, J., d'Allaines, C., Perrin, C., Pebrier, A., and Ricordeau, G.: Closure under Refrigeration of a Congenital Aortico-Pulmonary Defect. Arch. mal. coeur **49:** 42, Jan. 1956.

In a 4½-year-old girl, the communication proved to be located immediately next to the valves and the coronary ostia, and to have extremely thin walls, so that external ligation could not be attempted. The operation, therefore, was repeated internally under refrigeration; the circulation was interrupted for 5½ minutes. This led to ventricular fibrillation that was terminated by electric shock; no cerebral damage occurred.

LEPESCHKIN

Castro Farinas, E.: Surgical Treatment of Mitral Stenosis and its Results. Rev. españ. cardiol. **9:** 222, 1955.

The author had operated on 65 cases of mitral stenosis, and 86 per cent of these were improved. Atrial fibrillation and hemoptysis did not interfere with good results. Four cases were operated upon before rheumatic activity could be controlled, with good results. In many cases mobilization of the valves improved not only the stenosis but also a preexisting regurgitation. During valvular fracture marked electrocardiographic abnormalities appeared in all cases; these were attributed to mechanical injury and to obstruction of the coronary flow. Transient atrial fibrillation, which could be eliminated by Cedilanic, appeared in 4 cases.

LEPESCHKIN

Beck, C. S., and Leighninger, D. S.: Scientific Basis for the Surgical Treatment of Coronary Artery Disease. J. A. M. A. **159:** 1264 (Nov. 26), 1955.

Information gained from some 5,000 operations on the coronary blood vessels of dogs for the last 23 years has been transferred to work on the human patient. Dr. Beck's number one operation has been shown to add 4.7 ml. of blood per minute to an area of myocardium made ischemic by complete ligation of the artery that normally feeds this muscle. This amount of blood is of no importance if delivered to myocardium that is fed by a normally patent artery or an artery that is three quarters occluded. If the artery is totally occluded the quantity of blood is protective against electric instability. This is important because electric instability is the factor that kills about 90 per cent of the cases of coronary artery disease. The remaining 10 per cent of the patients who died from coronary artery disease died from extensive myocardial degeneration and they were in circulatory failure. The operation produces a more uniform distribution of oxygen to the myocardium. Mortality for the number one operation has been reduced to 6.6 per cent and the operation has relieved symptoms in 9 out of 10 patients. At present, it appears to prolong life. Total mortality in patients treated surgically so far has been 18 per cent and the authors compare this with mortality of 30 per cent in 88 comparable patients treated medically. In view of these findings, it is thought by the authors that the patient with coronary artery disease should be told there is a more effective treatment. Operation should be done early in the course of the disease before irreparable damage occurs in the myocardium.

KITCHELL

THROMBOEMBOLIC PHENOMENA

Marks, J.: Anticoagulant Therapy in Idiopathic Occlusion of the Axillary Vein. Brit. M. J. **1:** 11 (Jan. 7), 1956.

Idiopathic, or "stress," occlusion of the axillary vein, described by Paget in 1866 and by von Schroetter in 1884, is sometimes known as the Paget-Schroetter syndrome. Twelve cases were treated with anticoagulants. Unusual stress clearly preceded thrombosis in 6. The stress consisted of scraping a ceiling (in a painter), strenuous rowing (in 2), handling heavy packets above the head (in 1 storekeeper and perhaps a second), practicing hurdling.

Dividing the cases into those with pain in the axilla and those without, the author could demonstrate striking difference in the effect of therapy. In those with pain, the pain was removed and swelling was minimal after treatment. In the second group, the arm was usually as swollen and discolored after treatment as before.

Pulmonary embolism has been described as a complication in 4 cases in the literature and in 1 of the author's cases.

McKusick

Pratt, G. H.: Complications of Phenylbutazone in Treatment of Thrombophlebitis. Geriatrics **11:** 31 (Jan.), 1956.

In closely correlated studies of the treatment of acute thrombophlebitis with phenylbutazone, 12 of 39 patients, or 30 per cent, showed noticeable improvement in their symptoms on administration of this drug. Nine of these showed the good effect within 3 days. Five other patients showed slight improvement, but not enough for the drug to be considered specific. Twenty-one, or 54 per cent, did not improve clinically at a rate more rapid than would have been expected without any specific drug therapy. Nine, or 24 per cent of the patients, showed complications from the therapy. In 5, complications were serious enough so that the therapeutic test was discontinued. If phenylbutazone is used for treatment of thrombophlebitis, it should be discontinued in 48 to 72 hours if no great benefit is discerned. It appears that the effect of the drug in thrombophlebitis is analgesic and not specific, at least in the dosages used in this test. Use of this drug seems particularly contraindicated in the aged.

Rinzler

Ask-Upmark, E.: On the Laterality of Cerebral Embolies. Acta med. scandinav. **152:** 433 (July), 1955.

A series of 31 cases of cerebral embolus collected over a period of 10 years were studied regarding the laterality of the embolus. Of the unilateral cases, 7 were found on the right and 18 were located in the left hemisphere. The author notes 4 other observations, which it is said may or may not be related to this apparent predilection of arterial embolization for the left hemisphere: (1) Patients who have valvular lesions and are able to hear their own murmurs are more often apt to report that the murmur is louder in the left ear; (2) parasitic emboli reaching the nervous system by way of the arterial blood are more apt to lodge in the left eye rather than the right; (3) neoplastic cerebral emboli that have been reported in the literature have shown some predilection for the left side; (4) xanthelasma is more apt to involve the left eye than the right. In the series making up the cases reported, the emboli were associated with valvular lesions in most instances but, in a few, infarctions or thrombosis of the left atrium without valvular lesions was the source of the emboli.

Rosenbaum

VASCULAR DISEASES

Betz, E. and Mauler, R.: Disturbance of Peripheral Circulation in Valvular Heart Disease. Ztschr. Kreislaufforsch. **45:** 2 (Jan.), 1956.

The finger plethysmogram at fluid pressures of 10 and 28 mm. Hg shows in normal subjects spontaneous oscillations of 3 to 4 minutes' duration. These oscillations were present in 6 of 8 cases of aortic valvular disease but in none of 16 cases of mitral disease. The normal vasoconstriction after deep inspiration was present in only 4 of the latter cases.

Lepeschkin

Reichert, F. L.: Revised Concepts of the Treatment of Raynaud's Syndrome and Thromboangiitis Obliterans (Buerger's Disease). Am. J. Surg. **91:** 41 (Jan.), 1956.

On the basis of the results obtained in 6 patients with Raynaud's syndrome and 3 with thromboangiitis obliterans, the author suggested the use of nutritional supplements and desiccated endocrine tablets of the anterior pituitary and the suprarenal cortex. He also suggested the use of rauwolfia root or its alkaloid, reserpine, for the suppression of of sweating in such conditions as thromboangiitis obliterans.

Abramson

OTHER SUBJECTS

Davidson, J., and Friddes, F. S.: Prolonged Activity and Movement after a Penetrating Stab Wound of the Heart. Brit. M. J. **1:** 210 (Jan. 28), 1956.

After a stab wound of the heart that led subsequently to fatal hemopericardium the patient was able to walk unaided a distance of about 600 yards in about 20 minutes. He died about 90 minutes after the stabbing, before reaching the hospital. This case and similar ones previously reported have main pertinence to forensic medicine; they explain an otherwise unaccountable or misleading dis-

crepancy between the alleged locus of an assault and the situation of the body when found.

McKusick

Weiss, E.: Consequences of Anxiety: The Emotions and the Heart. Geriatrics **11:** 151 (Apr.), 1956.

Cardiac neurosis may be found in people with normal hearts and in those with diseased hearts. Cardiac neurosis in persons with normal hearts may arise through anxieties caused by rejection for life insurance, a dramatic case of heart disease in some member of the family, some protracted emotional disturbance, or the appearance of an extrasystole or chest pain. When anxieties arise the chief symptoms may be grouped as follows: (1) pain and distress in the heart region; (2) dyspnea and fatigue; (3) palpitation or heart consciousness; and (4) tachycardia and other disturbances of rhythm. Anxiety in relation to the diseased heart is a more important problem because cardiac insufficiency can be prevented or postponed if the physician can deal successfully with emotional stress.

Rinzler

Monge, C. C., Cazorla, Y. A., Whittemburg, M. G., Sakota, B. Y., and Rizo-Patroń, C.: A Description of the Circulatory Dynamics in the Heart and Lungs of People at Sea Level and at High Altitude by Means of the Dye Dilution Technique. Acta physiol. latino-am. **5:** 198 (Dec.), 1955.

The high-altitude male native group shows longer circulation time, slightly greater cardiac output, greater blood volume, and greater quantity of blood in the lungs. When the amount of blood in the lungs (calculated by Newman's formula) is expressed as total blood volume, the high-altitude group also shows a higher figure over the sea-level group. The results are related to previous observations that Peruvian natives born and living at high altitude have a larger chest and a greater vital capacity than men living at sea level.

Aviado

Lammerant, J., Schrevel, J., and De Visscher, M.: Massive Arterial Hemorrhage in Chronic Cor Pulmonale. Acta cardiol. **11:** 29 (Fasc. 1), 1956.

In a case of chronic cor pulmonale with hypervolemia and polycythemia blood volume determinations with P^{32}-labeled red cells were performed before and subsequent to a massive arterial hemorrhage. Although the estimated blood loss amounted to 48 per cent of the original blood volume, shock did not develop. Analysis of all data suggested the hypervolemia and redistribution of interstitial edema fluid acted as efficient protective factors. However, the tolerance to the extensive blood loss was not complete as became evident from ischemic electrocardiographic alterations that developed in the precordial leads. Mechanisms that may be responsible for posthemorrhagic coronary insufficiency and polyuria are discussed.

Pick

Reubi, F., and Schmid, A.: Can Cardiac Output Be Determined by the Method of Starr (1954). Cardiologia **28:** 197 (Fasc. 3), 1956.

In 60 normal and hypertensive persons cardiac output calculated by Starr's formula was compared with results of determinations by the Fick method. In addition, these data were compared with calculations based solely on pulse pressure values, and in 41 cases with results obtained by the method of Wezler and Boeger. All 3 methods of calculation yielded values corresponding to 57 to 67 per cent of those obtained by the Fick principle and the deviations were similar in the same patient provided the diastolic pressure remained constant. No consistent correlation could be established between results obtained by Starr's and Fick's methods.

Pick

Horvath, S. M., Radcliffe, C. E., Hutt, B. K., and Spurr, G. B.: Metabolic Responses of Old People to a Cold Environment. J. Appl. Physiol. **8:** 145 (Sept.), 1955.

A general belief is that older individuals complain of chilliness more readily than do younger ones and that they frequently require more clothing. This decreased ability to withstand heat has been related to the diminished basal heat production observed in the aged. In order to determine the validity of these impressions, the present studies on aged individuals exposed to a moderately cold environment were performed.

Eight subjects varying in age from 52 to 76 years were exposed nude to a 10 C. environment. By means of copper constantan thermocouples, temperatures were recorded from the skin of the chest, upper arm, thigh, calf, index finger, great toe, and rectum. Expired air was collected in a Tissot spirometer and samples analyzed for O_2 and CO_2. From these data, respiratory minute volume, O_2 consumption, CO_2 production, and R.Q. were calculated. Central observations were made on a nude subject in a room having an ambient temperature of 28 $\pm$ 1 C. The subject was then covered with 3 woollen blankets and the observations repeated. The next observations were made after moving the patient into a room at 10 C. The blankets were kept on her for 10 minutes and then removed for 10 to 49 minutes. At the conclusion of the cold exposure, the subject was returned to the control environment for 30 minutes of observations. Similar studies were accomplished on 7 younger subjects ranging in age from 22 to 27 years.

The older subjects generally did not shiver or complain of the cold and reported little discomfort. This was in contrast to the marked shivering and complaints made by the younger subjects. In the

aged group there was no significant change in minute volume of respiration, O_2 consumption, heat production, or R.Q. There were significant increases in all these parameters in the younger group. Peripheral vasoconstriction occurred rapidly in both the aged and younger groups.

The body temperatures of the aged subjects did not differ from those found in the younger people. The lack of discomfort and shivering in the aged with a smaller decrease in mean body temperature as compared to younger people suggests that shivering does not necessarily compensate for the increased heat lost by convection.

These results do not support the concept that in the aged there is less power of compensation for changes in external temperature.

WECHSLER

Perkins, J. F., Jr., Adams, W. E., and Flores, A.: Arterial Oxygen Saturation vs. Alveolar Oxygen Tension As a Measure of Venous Admixture and Diffusion Difficulty in the Lung. J. Appl. Physiol. **8:** 455 (Jan.), 1956.

This study deals with the use of the 2-color compensated ear oximeter, the Pauling oxygen analyzer and the Rohn alveolar sampler for tests of pulmonary function. The procedure involves plotting arterial oxygen saturation against oxygen tension of alveolar air as the patient or animal breathes each of several concentrations of oxygen in nitrogen. The resulting curve lies in close proximity to an in vitro oxygen dissociation curve but this curve is altered by pulmonary or congenital heart disease.

With anatomic right-to-left shunting of blood past normal lung, the knee of the saturation tension curve is depressed and the right part of the curve rises in essentially linear fashion due to the addition to the arterial blood of O_2 dissolved in blood traversing normal lung. With a shunt-like effect due to distribution difficulty as in emphysema, the knee of the curve is also shifted downward due to admixture of blood from poorly ventilated alveoli, but the right part of the curve rises less and less steeply, rather than in linear fashion. With diffusion difficulty, the curve is shifted to the right, more so in exercise, as a result of the accompanying elevation in alveolo-end capillary oxygen diffusion gradient.

These effects were studied in anesthetized dogs with experimentally produced pulmonary lesions of known severity, in normal subjects and in patients with various types of pulmonary diseases. The results indicate that this is a method in patients for diagnosis and semi-quantitative evaluation of the severity of anatomic right-to-left shunting, shunt-like effect due to distribution difficulty, and diffusion difficulty.

WECHSLER

Keist, B. F., Sheeley, W. F., Byers, J. M., and Chinn, H. I.: Effect of Head Immobilization on Incidence of Airsickness. J. Appl. Physiol. **8:** 369 (Jan.), 1956.

Tilting one's head while the entire body is rotated about a vertical axis is known to cause nausea. It has been reported that head movements increase an individual's susceptibility to motion and conversely, that head restraint decreases such susceptibility. Because of these thoughts, and since motion sickness can be hazardous, it seemed appropriate to test the effectiveness of head immobilization alone and with drugs that prevent motion sickness in some people.

One-hundred and twelve experienced U. S. Army paratroopers were subjects. Each subject was given a capsule with either a lactose placebo or 0.65 mg. of hyoscine hydrobromide 1 hour before flight. In the airplane every other man had a helmet minimizing head movement. Each plan load thus contained an equal number of men receiving: (a) head rest plus hyoscine, (b) head rest plus placebo, (c) hyoscine without head rest, and (d) placebo without head rest. The planes flew in formation for 2 hours at an altitude of approximately 1,000 feet. During the entire flight, vomiting, pallor, or other indications of sickness were recorded by observers. This procedure was repeated in the same subjects for 4 consecutive days, but the treatment was changed each day.

These studies showed that hyoscine significantly ($p < 0.01$) decreased the incidence of vomiting in the placebo group from 31 per cent to 6.6 or 7.5 per cent. Diminished head motions failed to confer any protection in any group.

These results fail to confirm previous studies on the efficacy of head immobilization in preventing airsickness. This difference could be attributed to the bulky gear the paratroopers carried, duration of flight, turbulence, vibration, and flight pattern.

A study of the effects of head immobilization with and without 0.65 mg. of hyoscine hydrobromide was accomplished on 112 paratroopers during 4 2-hour flights. The results indicated the effectiveness of hyoscine and the failure of head support in decreasing the incidence of air sickness.

WECHSLER

Chandler, C. A., Rammelkamp, C. H., Krause, R. M., Kohen, R. J., and Perry, W. D.: Epidemic Acute Nephritis: Studies on Etiology, Natural History and Prevention. Medicine **34:** 431, 1955.

This report is based upon a study of a large outbreak of acute glomerulonephritis during a respiratory disease epidemic in a naval training station. This afforded an opportunity to test a recently advanced hypothesis that certain streptococcal strains of serologic type 12 may be "nephrito-

genic," in contrast to other strains. Of 367 patients studied, 184 had type 12 streptococci in throat cultures. The rest were infected with types 3, 6, 19, and other types, except for 37 who had negative cultures.

Acute glomerulonephritis occurred in 12 per cent of 184 patients convalescing from type 12 streptococcal pharyngitis, and in none of 146 patients convalescent from other types. The nephritis occurred after a latent period of 6 to 16 days, with a mean of 10 days. This is somewhat shorter than the latent period usually reported for acute rheumatic fever. However, in the latter disease the latent period is reckoned to the time of onset of symptoms, whereas in the present study hematuria often antedated symptoms by several days. The incidence of nephritis was higher than the reported incidence of acute rheumatic fever following infection with whatever type of streptococcus.

These findings speak for the existence of separate pathogenetic mechanisms for acute rheumatic fever and acute nephritis. The coexistence of the 2 conditions was not found more frequently than could be explained by chance alone. If the mechanisms were similar or related, it would have been expected to observe rheumatic fever more frequently among the patients developing acute nephritis and vice versa. Although the present study can not afford a satisfactory explanation of the nephritogenic capacity of type 12, or the mechanism of acute glomerulonephritis, the latent period between infection and nephritis suggests that some immune response is involved. The study suggests an enhanced antibody response in the patients who developed nephritis as compared with those who had normal convalescence, but the data do not permit the development of nephritis to be attributed to increased antibody formation.

Early treatment with penicillin definitely reduced the incidence of acute nephritis, but later treatment was ineffective. On the other hand, penicillin treatment begun as late as the ninth day may prevent the occurrence of rheumatic fever. Gamma globulin therapy resulted in increased antibody formation and an apparent increase in the attack rate for glomerulonephritis, but these results may have been due to chance variation. The renal disease was generally mild and tended to subside within 8 to 10 weeks.

ENSELBERG

Finnerty, F. A., Jr.: Toxemia of Pregnancy as seen by an Internist: An Analysis of 1,081 Patients. Ann. Int. Med. **44:** 358 (Feb.), 1956.

Serial studies on 1,081 "toxemia-suspect" patients have revealed that hypertensive vascular disease and pyelonephritis frequently masquerade as toxemia of pregnancy. The triad (or any part) of an elevated blood pressure, edema, and albuminuria has been seen in each of these diseases. Experience has suggested that ophthalmoscopic examination and a complete urinalysis permit prompt differentiation of these diseases. Toxemia is said to exist when the ophthalmoscopic examination reveals a retinal sheen and normal arteries and urinalysis reveals only albuminuria. Hypertensive vascular disease exists when the retinal arteries show hypertensive changes and no retinal sheen is present. When both hypertensive changes and a retinal sheen are seen on ophthalmoscopic examination, with or without albuminuria, toxemia is then superimposed on hypertensive vascular disease. The finding of normal fundi and albuminuria suggests pyelonephritis; clumps of white cells and glitter cells document the diagnosis. Though a retinal sheen and albuminuria are seen in both toxemia and acute glomerulonephritis, microscopic hematuria (occasionally gross hematuria) is seen more commonly in glomerulonephritis. Though 95 per cent of the patients referred to the clinic were originally diagnosed as toxemia, only 13 per cent had toxemia by our criteria. The diagnoses included hypertensive vascular disease (666 cases), hypertensive vascular disease plus superimposed toxemia (90 cases), postpartum hypertension (72 cases), pure toxemia (154 cases), pyelonephritis (56 cases), edema without disease (38 cases), and unrelated cardiac or renal disease (5 cases). The ability to differentiate these disease states provided the opportunity to study whether toxemia caused vascular damage. One hundred twenty-five of the pure toxemia group 6 weeks postpartum revealed no abnormality. In 29 patients, however, despite return of the blood pressure to normal and disappearance of edema and albuminuria, examination of the retina revealed definite retinopathy. These retinal changes are attributed to the duration of the toxemia rather than to its severity.

WENDKOS

Hermanutz, N.: Clinical Investigations Concerning the Importance of Spleen and Liver for the Circulation and the Heart. Arch. Kreislaufforsch. **23:** 1 (Fasc. 1–3), 1955.

In order to investigate the role of the spleen and liver in the regulation of the circulation the author studied 19 cases subsequent to splenectomy and 33 cases with traumatic lesions of the liver.

Electrocardiographic and hemodynamic data at rest and after exercise performed under normal breathing conditions and in low pressure chambers revealed no abnormalities attributable to abnormal cardiovascular function. Thus a failure of circulatory regulation by a partial loss of the liver-spleen system could not be demonstrated.

PICK

AMERICAN HEART ASSOCIATION, INC.

44 East 23rd Street, New York 10, N. Y.

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ABSTRACTS OF AHA SCIENTIFIC SESSIONS PAPERS DUE JUNE 15

Those wishing to present either papers or scientific exhibits at the 1957 Scientific Sessions of the American Heart Association in Chicago next fall must make application before June 15. The Scientific Sessions are scheduled for October 25–28 at the Hotel Sherman, in conjunction with the 33rd Annual Meeting of the Association.

Papers intended for presentation must be based on original investigation in, or related to, the cardiovascular field. Abstracts must be submitted in triplicate on forms obtainable from the Medical Director of the Association. Abstracts should not exceed 300 words and should contain in summary form the results obtained and the conclusions reached.

Space will be available at the Hotel Sherman for scientific and technical exhibits. Applications for space should also be addressed to the AHA Medical Director (44 East 23rd Street, New York 10, N. Y.). Applications will be processed by the Program Committee of the Scientific Council.

REVISED RHEUMATIC FEVER PREVENTION RECOMMENDATIONS AND THROAT CULTURE STATEMENT AVAILABLE

Revised recommendations for prevention of first and repeat attacks of rheumatic fever, which were published in the January 1957 issue of *Circulation*, are available from the American Heart Association and its affiliates. The statement, reprinted in leaflet form, is entitled "Prevention of Rheumatic Fever and Bacterial Endocarditis Through Streptococcal Infections." Schedules for treatment of streptococcal infections in the general population and for prevention of such infections in rheumatic individuals are contained in a wallet card.

Principal changes in the recommendations refer to monthly injections of 1,200,000 units of benzathin penicillin G intramuscularly which is listed first among prophylactic methods; to the duration of prophylaxis; and to the value of throat cultures in diagnosing streptococcal infections.

"A Method for Culturing Beta-Hemolytic Streptococci from the Throat" is a new statement available from the Association. It was prepared by Lewis W. Wannamaker, M.D., at the request of the Committee on Prevention of Rheumatic Fever and Bacterial Endocarditis of the Council on Rheumatic Fever and Congenital Heart Disease. The statement deals with the value of throat cultures to the practicing physician, with technics of obtaining throat cultures and of streaking and reading plates.

NEW PROFESSIONAL FILM SHOWS DISORDERS OF HEART BEAT

"Disorders of the Heart Beat" is the title of new 22-minute professional film produced in color for the American Heart Association and its affiliates by Churchill-Wexler, Los Angeles. The motion picture explains the theory of how abnormal heart beats develop and how these look on the electrocardiogram. The sounds of arrhythmias are recorded and the phonogram pictures the heart sounds. The new film will be available—on a loan or rental basis—from local Heart Associations.

LEAFLET FOR HYPERTENSIVES ISSUED

"Your Blood Pressure" is the title of a new American Heart Association leaflet which physicians may wish to distribute to their hypertensive patients. The illustrated leaflet, copies of which can be obtained from local Heart Associations, contains basic facts on hypertension and stresses that "it takes two to treat your hypertension—your doctor and you." It also urges patients to follow their physician's advice carefully and to cooperate during trial periods of new medicines.

HIGH BLOOD PRESSURE COUNCIL NAMES LEADERS

Meyer Friedman, M.D., Director, Harold Brunn Institute of Cardiovascular Research, Mt. Zion Hospital, San Francisco, has been elected Chairman of the Medical Advisory Board of the Council for High Blood Pressure Research of the American Heart Association.

The officers of the Council were re-elected for another term: Maynard Hale Murch as President, Frank E. Joseph as Vice President, George E. Merrifield as Secretary, and I. F. Freiberger as Treasurer.

BOARD OF DIRECTORS HONORS FOUR PHYSICIANS

Among the 6 American Heart Association leaders who received Awards of Merit for "noteworthy contributions in the development of the Association's national program" at the Board of Directors meeting in Chicago last December were four physicians: Dr. William H. Bunn, former President of the Youngstown Area Heart Association, who has served as a member of the national Board of Directors, as Vice President and as Secretary of the Association; Dr. David D. Rutstein, Harvard Medical School, a former Medical Director of the Association, now a Vice President; Dr. Sidney Strauss, Chicago, over a period of 30 years variously a member of the Association's first Board of Directors, founder of the Illinois Heart Association and past President of the Chicago Heart Association; Dr. Harry E. Ungerleider, Equitable Life Assurance Society, New York, a former Secretary of the National Association and a Board member of the American and New York Heart Associations for 14 years.

UTAH HEART ASSOCIATION ESTABLISHES PROFESSORSHIP IN CARDIOLOGY

The Utah Heart Association has established and is supporting the first professorship in cardiology at the Utah School of Medicine. It will be known as the Louis E. Viko Chair of Cardiology, in honor of Dr. Louis E. Viko of Salt Lake City, past President of the Utah Heart Association. The professorship will be filled by Dr. Hans H. Hecht of Salt Lake City. Dr. Hecht is Associate Professor of Medicine at the University and Director of the Heart Station at the Salt Lake General Hospital. The New Chair for cardiology is the latest in a growing number of such professorships which are established and supported by local Heart Associations as valuable additions to schools of medicine.

ABSTRACTS OF SCIENTIFIC SESSIONS AND LIPOPROTEIN STUDY AVAILABLE

Abstracts of papers presented at the 29th Scientific Sessions of the American Heart Association in Cincinnati, October 26–29, 1956 are available from the National Office (Price, $1.00).

A special supplement to the October, 1956 issue of *Circulation*, entitled "Evaluation of Serum Lipoprotein and Cholesterol Measurements as Predictors of Clinical Complications of Atherosclerosis—Report of a Cooperative Study of Lipoproteins and Atherosclerosis" can be obtained from the American Heart Association, free of charge.

SEND SUBSCRIPTION RENEWAL ORDERS TO GRUNE AND STRATTON, INC.

Renewal orders for the journals of the American Heart Association, *Circulation* and *Circulation Research*, should be sent directly to the publisher, Grune and Stratton, Inc., 381 Fourth Ave., New York 16, N. Y., who has been authorized by the Association to handle all subscriptions to these journals, whether from members of the Association, or from nonmembers.

MEETINGS CALENDAR

February 14: Symposium on Present Status of Heart Sound Production and Recording, University of Buffalo, Buffalo, N. Y.

March 4–6: National Biophysics Conference, Columbus, Ohio. Samuel A. Talbot, Department of Medicine, Johns Hopkins Hospital, Baltimore 5, Md.

March 11: Scientific Meeting of the New England Cardiovascular Society, Boston. Alexander S.

Nadas, M.D., Secretary, The New England Cardiovascular Society, % The Massachusetts Heart Association, 650 Beacon St., Boston 15, Mass.

March 19: National Advisory Committee of Local Health Departments, Cincinnati. Miss Martha Luginbuhl, National Advisory Committee, 1790 Broadway, New York, N. Y.

March 20–22: Annual Meeting of the National Health Council, Cincinnati. National Health Forum Registration, National Health Council, 1790 Broadway, New York, N. Y.

March 25–28: American Academy of General Practice, St. Louis. Mr. Mac F. Cahal, Volker Blvd., Kansas City 12, Mo.

April 8–12: American College of Physicians, Boston. Mr. E. R. Loveland, 4200 Pine St., Philadelphia, Pa.

April 11–13: American Association of Pathologists and Bacteriologists, Washington, D. C. Edward A. Gall, Cincinnati General Hospital, Cincinnati 29, Ohio.

April 15–19: American Society for Experimental Pathology, Chicago. Cyrus C. Erickson, 858 Madison Ave., Memphis 3, Tenn.

April 22–27: American Academy of Neurology, Boston. T. W. Framer, University of North Carolina, Chapel Hill, N. C.

April 28–May 2: Society for American Bacteriologists, Detroit. J. W. Bailey, Sterling-Winthrop, Research Institute, Rensselaer, N. Y.

May 5: American Federation for Clinical Research, Atlantic City, N. J. William W. Stead, Veterans Hospital, Minneapolis 17, Minn.

May 5–10: National Tuberculosis Association, Kansas City, Mo. Mrs. Morrell DeReign, 1790 Broadway, New York 19, N. Y.

May 6–9: American Urological Association, Pittsburgh. Samuel L. Raines, 188 S. Bellevue Blvd., Memphis, Tenn.

May 7–8: Association of American Physicians, Atlantic City, N. J. P. B. Beeson, Yale University School of Medicine, New Haven, Conn.

May 8–10: American Surgical Association, Chicago. R. Kennedy Gilchrist, 59 E. Madison St., Chicago, Ill.

May 13: Scientific Meeting of the New England Cardiovascular Society, Boston. Alexander S. Nadas, M.D., Secretary, The New England Cardiovascular Society, % The Massachusetts Heart Association, 650 Beacon St., Boston 15, Mass.

May 15–18: First Wisconsin Conference on Work and the Heart, Milwaukee. Elston L. Belknap, M.D., Marquette University School of Medicine, 561 N. 15th St., Milwaukee 3, Wis. (By invitation.)

May 27–29: American Gynecological Society, Hot Springs, Va. A. A. Marchetti, 3800 Reservoir Rd., N.W., Washington 7, D. C.

May 29–June 2: American College of Chest Physicians, New York. Murray Kornfeld, 112 E. Chestnut St., Chicago, Ill.

May 30–31: American Geriatrics Society, New York. Richard J. Kraemer, Greenwood, R. I.

June 1: American Academy of Tuberculosis Physicians, New York. Oscar S. Levin, P. O. Box 7011, Denver 6, Colo.

June 2: American Society for Vascular Surgery, New York. Henry Swan, 4200 East 9th Ave., Denver 20, Colo.

June 3–7: American Medical Association Annual Meeting, New York. George F. Lull, M.D., American Medical Association, 535 N. Dearborn St., Chicago 10, Ill.

June 16–21: American Society for Pediatric Research, Carmel, Calif. Sydney S. Gellis, 330 Brookline Ave., Boston 15, Mass.

June 17–19: American Pediatric Society, Carmel, Calif. A. C. McGuinness, 1427 Eye Street, N. W., Washington 5, D. C.

ABROAD

February 24–28: Biennial International Scientific Congress, International College of Surgeons, Mexico City. Dr. Max Thorek, International College of Surgeons, 850 Irving Rd., Chicago 13, Ill.

June 3–7: Harvey Tercentenary Congress, London. D. Geraint James, M.D., M.R.C.P., 11 Chandos Street, Cavendish Square, London W.1.

June 23–28: International Congress on Rheumatic Diseases, Toronto, Ont. International Congress on Rheumatic Diseases, P. O. Box 237, Terminal "A", Toronto, Ontario, Canada.

July 14–19: International Gerontological Congress, Merano-Bolzano, Italy. Segreteria, Quarto Congresso Internazionale de Gerontologia, Viale Morgagni 85, Firenze, Italy.

July 21–28: International Congress of Neurological Sciences, Brussels, Belgium. Pearce Bailey, M.D., National Institutes of Health, Bethesda 14, Md.

July 24–29: International Congress of Nutrition, Paris. Congress International de Nutrition, 71 Blvd. Pereire, Paris 17e, France.

September 14–21, 1958: Third World Congress of Cardiology, Brussels. Dr. F. Van Dooren, 80 Rue Mercelis, Brussels, Belgium.

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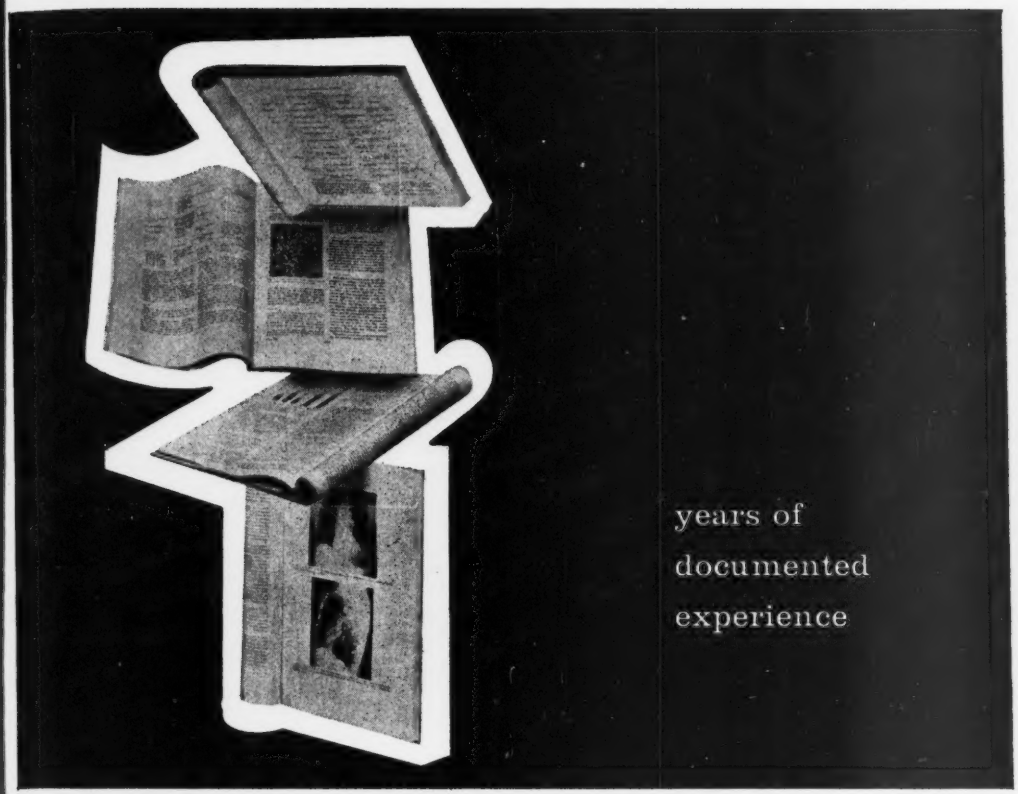

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